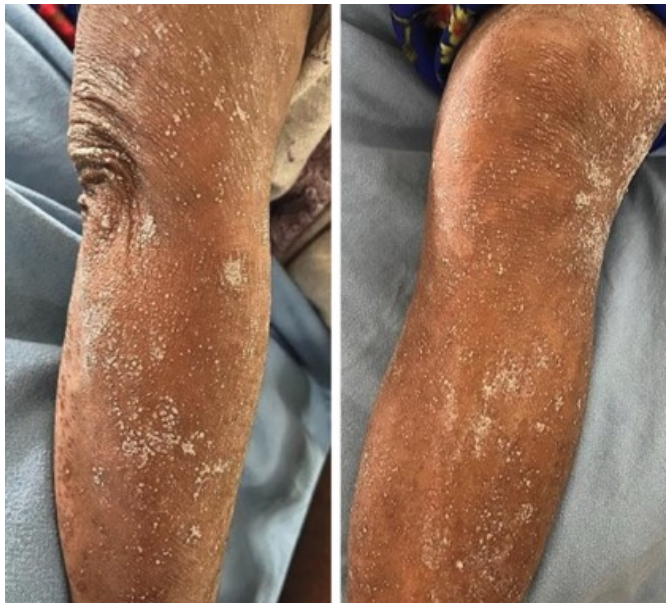
https://www.mdc-berlin.de/de/veroeffentlichungstypen/clinical-journal-club


Als gemeinsame Einrichtung von MDC und Charité fördert das Experimental and Clinical Research Center die Zusammenarbeit zwischen Grundlagenwissenschaftlern und klinischen Forschern. Hier werden neue Ansätze für Diagnose, Prävention und Therapie von Herz-Kreislauf- und Stoffwechselerkrankungen, Krebs sowie neurologischen Erkrankungen entwickelt und zeitnah am Patienten eingesetzt. Sie sind eingeladen, uns beizutreten. Bewerben Sie sich!



A 52-year-old woman with hypertension presented to the hospital with a 1-month history of fatigue, as well as 6 days of vomiting and 1 day of confusion. Over the past 20 years, she had not received regular treatment for hypertension. Physical examination was notable for pallor of the conjunctiva and oral mucosa, as well as for powdery, crystalline deposits on the arms, legs, trunk, and scalp. Which of the following is the most likely diagnosis?

Contact dermatitis

Pityriasis versicolor

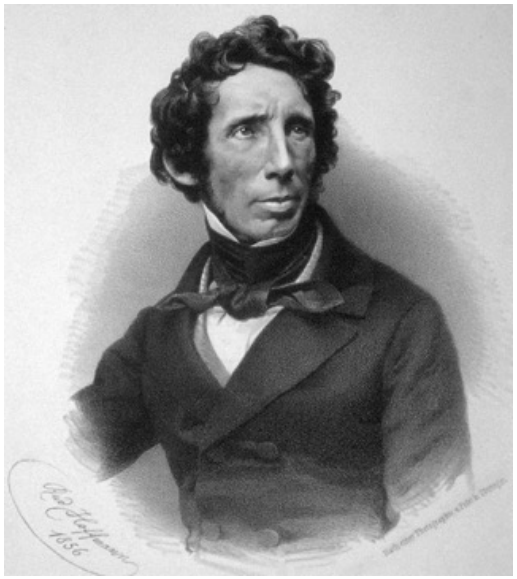
Psoriasis

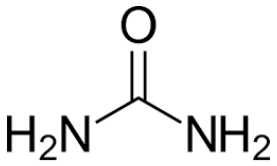
Uremic frost

Xerosis cutis

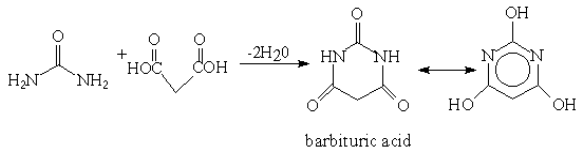
Laboratory studies in this patient showed markedly elevated levels of blood urea nitrogen (BUN) and creatinine. Analysis of a skin scraping of the powdery crystals was positive for urea. A diagnosis of advanced end-stage kidney disease with uremic frost was made. Uremic frost is a rare manifestation of end-stage kidney disease that may occur when the BUN level is greater than 200 mg per deciliter (71 mmol per liter). The whitish crystals form on the skin when sweat with a high content of urea evaporates. Treatment with hemodialysis for five consecutive sessions was initiated.

German chemist Friedrich Wöhler first synthesized urea from inorganic materials in 1828, a groundbreaking achievement that marked the start of modern organic chemistry. He achieved this by evaporating a solution of ammonium cyanate, which he had prepared by combining silver cyanate and ammonium chloride, disproving the vital force theory that organic compounds could only come from living organisms.





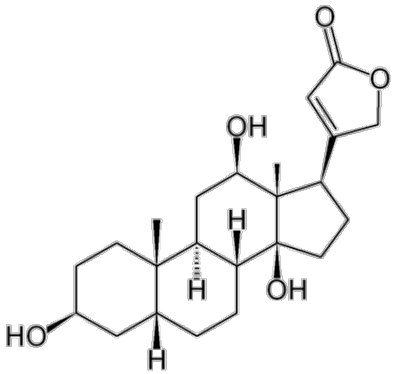

Weitere Entwicklungen

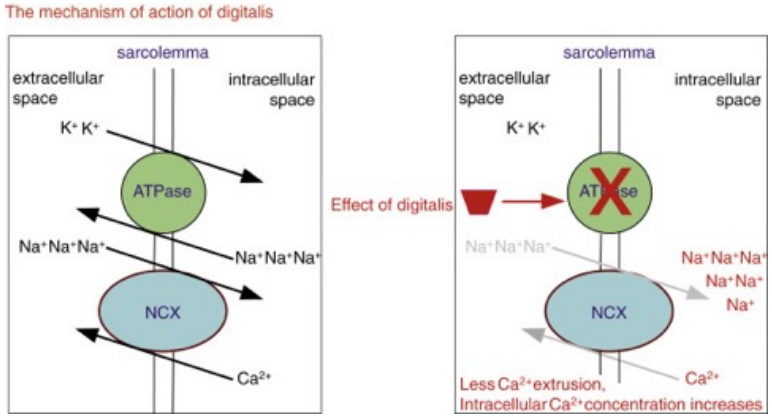



barbituric acid

English physician and botanist William Withering is credited with discovering and documenting the medical uses of digitalis, a drug derived from the foxglove plant. In 1785, he published An Account of the Foxglove and Some of Its Medical Uses, which detailed his successful clinical trials for treating congestive heart failure and described the drug's effects and toxicity.

Fingerhut

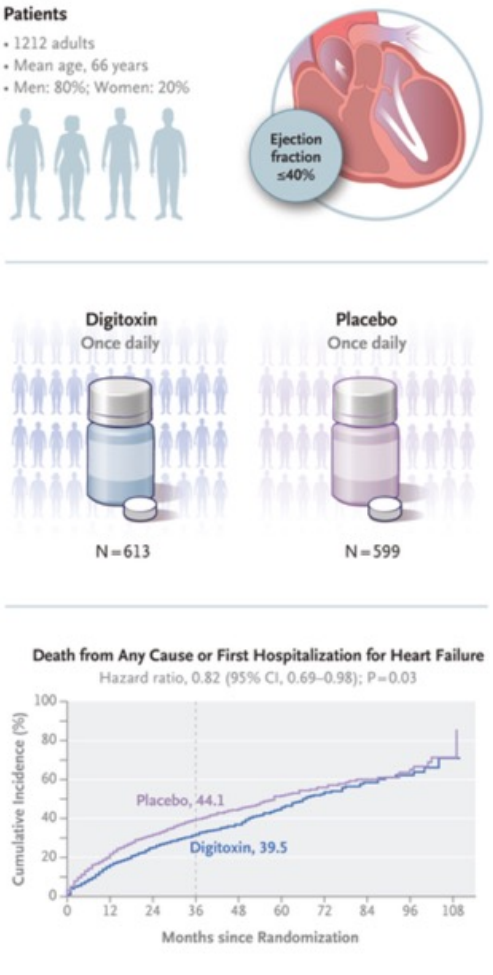


# Digitoxin in Patients with Heart Failure and Reduced Ejection Fraction

The therapeutic efficacy of the cardiac glycoside digitoxin in patients with heart failure and reduced ejection fraction is not established.

In this international, double-blind, placebo-controlled trial, we randomly assigned patients with chronic heart failure who had a left ventricular ejection fraction of 40% or less and a New York Heart Association (NYHA) functional class of III or IV or a left ventricular ejection fraction of 30% or less and an NYHA functional class of II in a 1:1 ratio to receive digitoxin (at a starting dose of 0.07 mg once daily) or matching placebo in addition to guideline-directed medical therapy. The primary outcome was a composite of death from any cause or hospital admission for worsening heart failure, whichever occurred first.



Unlike digoxin, digitoxin is effectively eliminated by enterohepatic excretion when renal function is markedly impaired. Digitoxin concentrations in blood can remain stable without dose adjustments, even among patients with progressive renal dysfunction. However, the lack of double-blind, randomized, clinical trials that use digitoxin underscores the need for further investigation. The DIGIT-HF (Digitoxin to Improve Outcomes in Patients with Advanced Chronic Heart Failure) trial was conducted to evaluate the efficacy and safety of digitoxin at low concentrations in patients with chronic heart failure and reduced ejection fraction that had been treated with current medical and cardiac device therapies.

**Patients**

Patients were eligible for enrollment if they were at least 18 years old, had symptomatic chronic heart failure (specified as a left ventricular ejection fraction of ≤40% and an NYHA functional class of III or IV, or a left ventricular ejection fraction of ≤30% and an NYHA functional class of II), and had received evidence-based therapy for heart failure for a period of at least 6 months.

**Trial Procedures**

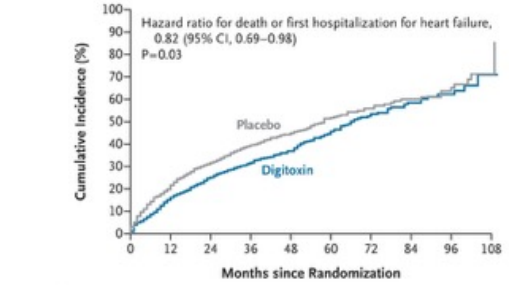
Patients were randomly assigned in a 1:1 ratio to receive digitoxin at a starting dose of 0.07 mg once daily or matching placebo. Digitoxin concentrations in serum were measured in a blinded manner, and if the level was found to be outside the predefined target range of 8 to 18 ng per milliliter (10.5 to 23.6 nmol per liter), the dosage was adjusted accordingly, with either a decrease to 0.05 mg once daily or an increase to 0.1 mg once daily.

| Characteristic | Digitoxin (N=613) | Placebo (N=599) |
|---|---|---|
| Age — yr | 66.0±11.1 | 65.8±11.4 |
| Female sex — no. (%) | 122 (19.9) | 125 (20.9) |
| Region — no. (%) | | |
| Germany | 545 (88.9) | 533 (89.0) |
| Austria | 19 (3.1) | 14 (2.3) |
| Serbia | 49 (8.0) | 52 (8.7) |
| NYHA functional class — no. (%)† | | |
| II | 181 (29.5) | 178 (29.7) |
| III | 408 (66.6) | 399 (66.6) |
| IV | 24 (3.9) | 22 (3.7) |
| Left ventricular ejection fraction — % | 28.4±6.9 | 28.9±6.7 |
| Left ventricular ejection fraction <30% — no. (%) | 315 (51.4) | 278 (46.4) |
| Main cause of heart failure — no./total no. (%) | | |
| Ischemic | 323/608 (53.1) | 310/592 (52.4) |
| Nonischemic or unknown | 285/608 (46.9) | 282/592 (47.6) |
| Body-mass index‡ | 29.3±5.7 | 28.9±5.6 |
| Heart rate — beats/min | 73.7±11.9 | 74.1±12.3 |
| Systolic blood pressure — mm Hg | 120.5±18.6 | 121.4±18.8 |
| Atrial fibrillation — no. (%) | 169 (27.6) | 161 (26.9) |
| eGFR | | |
| Mean — ml/min/1.73 $m^2$ | 65.0±23.0 | 65.2±23.7 |
| ≤60 ml/min/1.73 $m^2$ — no./total no. (%) | 263/612 (43.0) | 257/599 (42.9) |
| Device therapy — no./total no. (%) | | |
| Implantable cardioverter–defibrillator therapy | 415/613 (67.7) | 364/598 (60.9) |
| Cardiac-resynchronization therapy | 162/613 (26.4) | 144/597 (24.1) |
| Heart failure medication — no. (%) | | |
| Beta-blocker | 593 (96.7) | 567 (94.7) |
| Angiotensin-converting–enzyme inhibitor | 222 (36.2) | 213 (35.6) |
| Angiotensin-receptor blocker | 113 (18.4) | 115 (19.2) |
| Angiotensin receptor–neprilysin inhibitor | 248 (40.5) | 231 (38.6) |
| Mineralocorticoid receptor antagonist | 466 (76.0) | 458 (76.5) |
| Sodium–glucose cotransporter 2 inhibitor§ | 121 (19.7) | 113 (18.9) |
| Cardiac glycoside | 3 (0.5) | 6 (1.0) |

## Primary and Secondary Outcomes.

| Outcome | Digitoxin (N=613) | | Placebo (N=599) | | Hazard or Rate Ratio (95% CI)* |
|---|---|---|---|---|---|
| | *no. (%)†* | *events/100 patient-yr* | *no. (%)†* | *events/100 patient-yr* | |
| **Primary outcome and components** | | | | | |
| Death from any cause or first hospitalization for heart failure | 242 (39.5) | 12.8 | 264 (44.1) | 15.7 | 0.82 (0.69 to 0.98)‡ |
| Death from any cause | 167 (27.2) | 7.8 | 177 (29.5) | 8.9 | 0.86 (0.69 to 1.07)§ |
| First hospitalization for heart failure¶ | 172 (28.1) | 9.1 | 182 (30.4) | 10.8 | 0.85 (0.69 to 1.05) |
| **Key secondary outcome** | | | | | |
| Death from any cause and hospitalization for heart failure | 537 | 25.1 | 531 | 26.6 | 0.85 (0.67 to 1.09)‖ |
| **Other secondary outcomes** | | | | | |
| Death from cardiovascular causes | 125 (20.4) | 5.8 | 132 (22.0) | 6.6 | 0.87 (0.67 to 1.11) |
| Death from heart failure | 46 (7.5) | 2.2 | 47 (7.8) | 2.4 | 0.86 (0.57 to 1.31) |
| Sudden death from cardiac causes | 12 (2.0) | 0.6 | 12 (2.0) | 0.6 | 0.89 (0.40 to 2.00) |
| Death from noncardiovascular causes | 42 (6.9) | 2.0 | 45 (7.5) | 2.3 | 0.84 (0.55 to 1.29) |
| Hospitalization for cardiovascular causes¶ | 359 (58.6) | 28.8 | 353 (58.9) | 32.8 | 0.89 (0.77 to 1.04) |
| Hospitalization for noncardiovascular causes¶ | 263 (42.9) | 18.1 | 255 (42.6) | 18.6 | 0.97 (0.81 to 1.15) |
| Any hospitalization¶ | 429 (70.0) | 43.9 | 427 (71.3) | 50.4 | 0.90 (0.78 to 1.03) |
| Death from cardiovascular causes or first hospitalization for worsening heart failure | 220 (35.9) | 11.7 | 232 (38.7) | 13.8 | 0.85 (0.71 to 1.03) |

**A** Death from Any Cause or First Hospitalization for Heart Failure

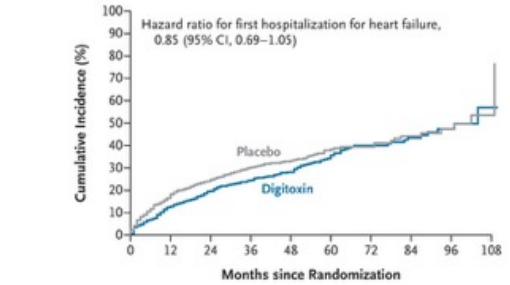



| No. at Risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | 599 | 421 | 309 | 234 | 184 | 126 | 78 | 47 | 24 | 4 |
| Digitoxin | 613 | 460 | 346 | 276 | 208 | 144 | 92 | 55 | 25 | 3 |

**B** Death from Any Cause


| No. at Risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | 599 | 485 | 370 | 291 | 229 | 162 | 103 | 60 | 29 | 4 |
| Digitoxin | 613 | 507 | 398 | 317 | 239 | 172 | 113 | 70 | 28 | 4 |

**C** First Hospitalization for Heart Failure

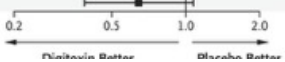


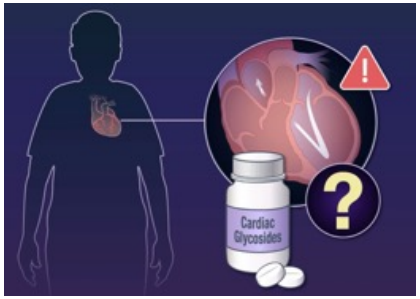

| No. at Risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | 599 | 421 | 309 | 234 | 184 | 126 | 78 | 47 | 24 | 4 |
| Digitoxin | 613 | 460 | 346 | 276 | 208 | 144 | 92 | 55 | 25 | 3 |

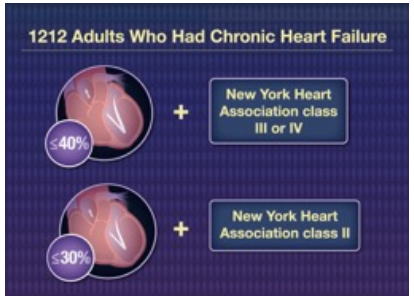
**Cardiovascular Outcomes.**

Panel A shows the cumulative incidence of death from any cause or first hospitalization for heart failure (the composite primary outcome). Panels B and C show the cumulative incidence of the two components of the primary outcome.

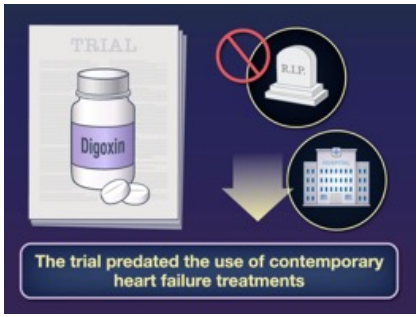
| Subgroup | Digitoxin | Placebo | Hazard Ratio for Primary-Outcome Event (95% CI) |
|---|---|---|---|
| | *no. of patients with event/total no. (%)* | | |
| All patients | 242/613 (39.5) | 264/599 (44.1) | 0.82 (0.69–0.98) |
| Sex | | | |
| Male | 200/491 (40.7) | 217/474 (45.8) | 0.84 (0.69–1.02) |
| Female | 42/122 (34.4) | 47/125 (37.6) | 0.73 (0.46–1.17) |
| NYHA functional class | | | |
| II | 57/181 (31.5) | 63/178 (35.4) | 0.76 (0.52–1.11) |
| III or IV | 185/432 (42.8) | 201/421 (47.7) | 0.83 (0.68–1.02) |
| Atrial fibrillation | | | |
| Yes | 67/169 (39.6) | 79/161 (49.1) | 0.72 (0.50–1.03) |
| No | 175/444 (39.4) | 185/438 (42.2) | 0.86 (0.69–1.06) |
| Geographic region | | | |
| Germany and Austria | 237/564 (42.0) | 256/547 (46.8) | 0.82 (0.68–0.97) |
| Serbia | 5/49 (10.2) | 8/52 (15.4) | 0.69 (0.22–2.19) |
| Age | | | |
| <70 yr | 116/362 (32.0) | 142/350 (40.6) | 0.77 (0.60–1.00) |
| ≥70 yr | 126/251 (50.2) | 122/249 (49.0) | 0.87 (0.67–1.14) |
| Ejection fraction | | | |
| <30% | 127/315 (40.3) | 130/278 (46.8) | 0.77 (0.59–0.99) |
| ≥30% | 115/298 (38.6) | 134/321 (41.7) | 0.85 (0.66–1.11) |
| Main cause of heart failure | | | |
| Ischemic | 144/323 (44.6) | 140/310 (45.2) | 0.97 (0.76–1.24) |
| Nonischemic or unknown | 97/285 (34.0) | 119/282 (42.2) | 0.70 (0.53–0.93) |
| Heart rate | | | |
| <75 bpm | 134/354 (37.9) | 143/348 (41.1) | 0.92 (0.72–1.18) |
| ≥75 bpm | 108/257 (42.0) | 121/251 (48.2) | 0.63 (0.48–0.83) |
| Systolic blood pressure | | | |
| ≤120 mm Hg | 131/331 (39.6) | 148/300 (49.3) | 0.61 (0.48–0.79) |
| >120 mm Hg | 111/282 (39.4) | 116/299 (38.8) | 1.03 (0.78–1.36) |
| Body-mass index | | | |
| <30 | 142/374 (38.0) | 170/369 (46.1) | 0.74 (0.58–0.93) |
| ≥30 | 99/238 (41.6) | 94/229 (41.0) | 0.91 (0.67–1.23) |
| Hypertension | | | |
| Yes | 210/492 (42.7) | 212/468 (45.3) | 0.86 (0.71–1.05) |
| No | 32/121 (26.4) | 52/129 (40.3) | 0.57 (0.34–0.93) |
| Diabetes mellitus | | | |
| Yes | 106/222 (47.7) | 106/231 (45.9) | 0.93 (0.70–1.25) |
| No | 136/390 (34.9) | 157/367 (42.8) | 0.76 (0.60–0.96) |
| eGFR | | | |
| ≤60 ml/min/1.73 m² | 132/263 (50.2) | 142/257 (55.3) | 0.73 (0.56–0.94) |
| >60 ml/min/1.73 m² | 110/349 (31.5) | 122/342 (35.7) | 0.81 (0.62–1.06) |
| Implantable cardioverter–defibrillator therapy | | | |
| Yes | 179/415 (43.1) | 162/364 (44.5) | 0.94 (0.75–1.16) |
| No | 63/198 (31.8) | 101/234 (43.2) | 0.57 (0.41–0.80) |
| Cardiac-resynchronization therapy | | | |
| Yes | 84/162 (51.9) | 65/144 (45.1) | 1.03 (0.73–1.45) |
| No | 158/451 (35) | 198/453 (43.7) | 0.72 (0.58–0.90) |
| Mineralocorticoid receptor antagonist | | | |
| Yes | 166/466 (35.6) | 189/458 (41.3) | 0.82 (0.67–1.02) |
| No | 76/147 (51.7) | 75/141 (53.2) | 0.97 (0.68–1.38) |
| Angiotensin receptor–neprilysin inhibitor | | | |
| Yes | 81/248 (32.7) | 83/231 (35.9) | 0.80 (0.58–1.11) |
| No | 161/365 (44.1) | 181/368 (49.2) | 0.84 (0.67–1.05) |
| Sodium–glucose cotransporter 2 inhibitor | | | |
| Yes | 24/121 (19.8) | 32/113 (28.3) | 0.70 (0.40–1.23) |
| No | 32/98 (32.7) | 36/96 (37.5) | 0.59 (0.34–1.04) |
| Triple therapy | | | |
| Yes | 159/436 (36.5) | 178/422 (42.2) | 0.81 (0.65–1.01) |
| No | 83/177 (46.9) | 86/177 (48.6) | 0.89 (0.64–1.23) |
| Quadruple therapy | | | |
| Yes | 20/101 (19.8) | 28/99 (28.3) | 0.77 (0.41–1.42) |
| No | 36/118 (30.5) | 40/110 (36.4) | 0.64 (0.39–1.07) |



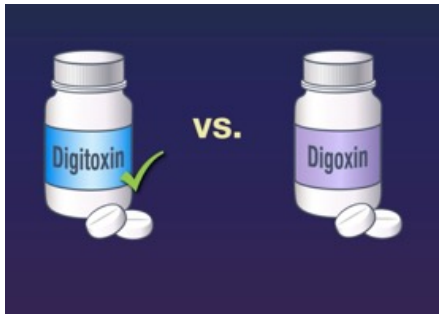


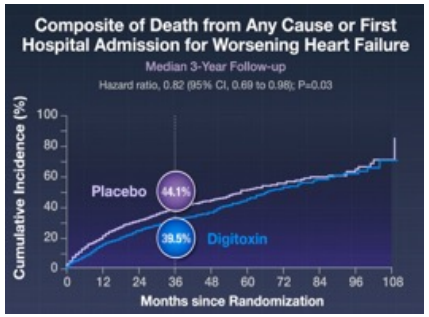







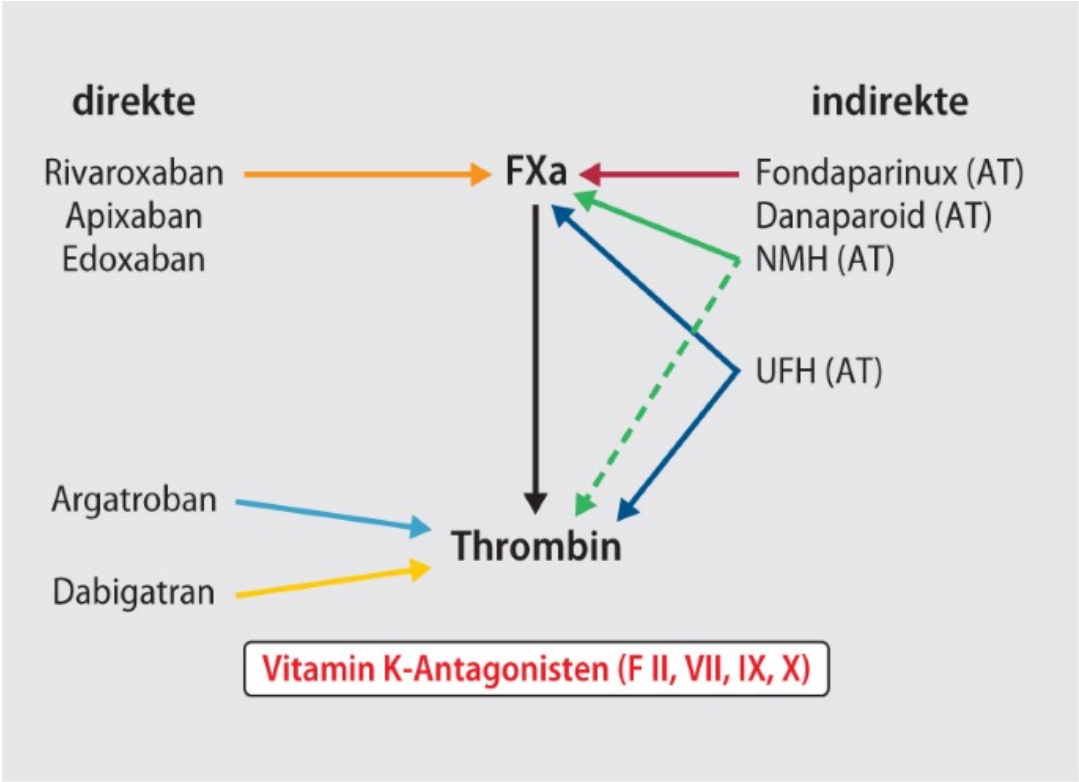



Independent of renal function

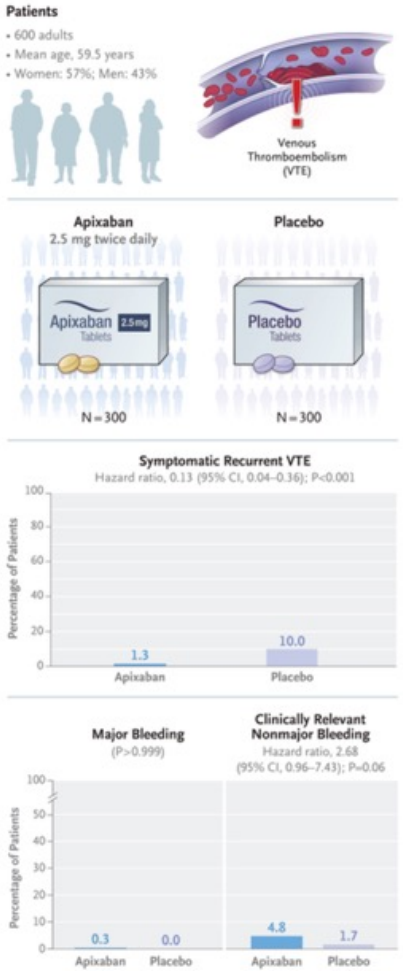
Apixaban hemmt Faktor Xa, indem es direkt an dessen aktives Zentrum bindet und es dadurch blockiert. Diese Hemmung verhindert die Umwandlung von Prothrombin zu Thrombin, wodurch die Bildung von Blutgerinnseln unterbunden wird. Apixaban wirkt reversibel und selektiv, sowohl auf freien als auch auf gerinnungsgebundenen Faktor Xa, und benötigt keine zusätzliche Bindung an Antithrombin III für seine Wirkung.



# Apixaban for Extended Treatment of Provoked Venous Thromboembolism

The appropriate duration of anticoagulation for venous thromboembolism (VTE) in patients who have a transient provoking factor (e.g., surgery, trauma, or immobility) and concomitant enduring risk factors is uncertain.

In this single-center, double-blind, randomized trial, adults with VTE after the occurrence of a transient provoking factor who had at least one enduring risk factor and had completed at least 3 months of anticoagulation were assigned to receive oral apixaban (at a dose of 2.5 mg twice daily) or placebo for 12 months. The primary efficacy outcome was the first symptomatic recurrent VTE. The primary safety outcome was the first episode of major bleeding according to the criteria of the International Society on Thrombosis and Hemostasis.



Venous thromboembolism (VTE) has traditionally been categorized as provoked (occurring after such transient risk factors as surgery, trauma, or immobility) or unprovoked (occurring without a readily identifiable trigger). Extended-duration anticoagulation is commonly prescribed for patients with unprovoked VTE because of a high risk of recurrence (6 to 10% per year) after the discontinuation of anticoagulation. For patients with provoked VTE who do not have cancer or severe thrombophilia, the recurrence risk is lower. In such patients, guidelines typically recommend 3 months of anticoagulation. In the commonly encountered population of patients with provoked VTE and concomitant enduring risk factors (e.g., autoimmune disorders, chronic lung disease, or obesity), the appropriate duration of anticoagulation is unclear.

We performed the Extended-Duration Low-Intensity Apixaban to Prevent Recurrence in High-Risk Patients with Provoked Venous Thromboembolism (HI-PRO) trial to assess the efficacy and safety of oral apixaban (at a dose of 2.5 mg twice daily), as compared with placebo, for the prevention of recurrence in patients with provoked VTE and at least one enduring risk factor.

**Trial Population**

Patients were required to be at least 18 years of age and to have objectively confirmed VTE with at least one provoking factor, including major surgery, trauma, acute medical illness, or immobility. At the time of screening, all the patients had been receiving anticoagulation for at least 3 months and had at least one enduring risk factor for recurrence, such as a body-mass index of at least 30, chronic lung disease, or chronic inflammatory disease.

## Randomization and Trial Intervention

We performed randomization using a permuted block size of 4, with 1:1 assignment to apixaban or placebo. A variable assignment sequence within blocks was generated by a centralized computer algorithm.

## Follow-up

Virtual trial visits were conducted every 3 months in addition to an in-person visit at 12 months. At each visit, patients were assessed for medication adherence, serious adverse events, adverse drug reactions, and trial outcomes.

## Outcome Measures

The primary efficacy outcome was the first symptomatic, recurrent, objectively confirmed VTE — which was defined as a composite of deep-vein thrombosis, pulmonary embolism, or both — during the 12 months after randomization, as measured in a time-to-event analysis.

## Demographic and Clinical Characteristics of the Patients at Baseline.

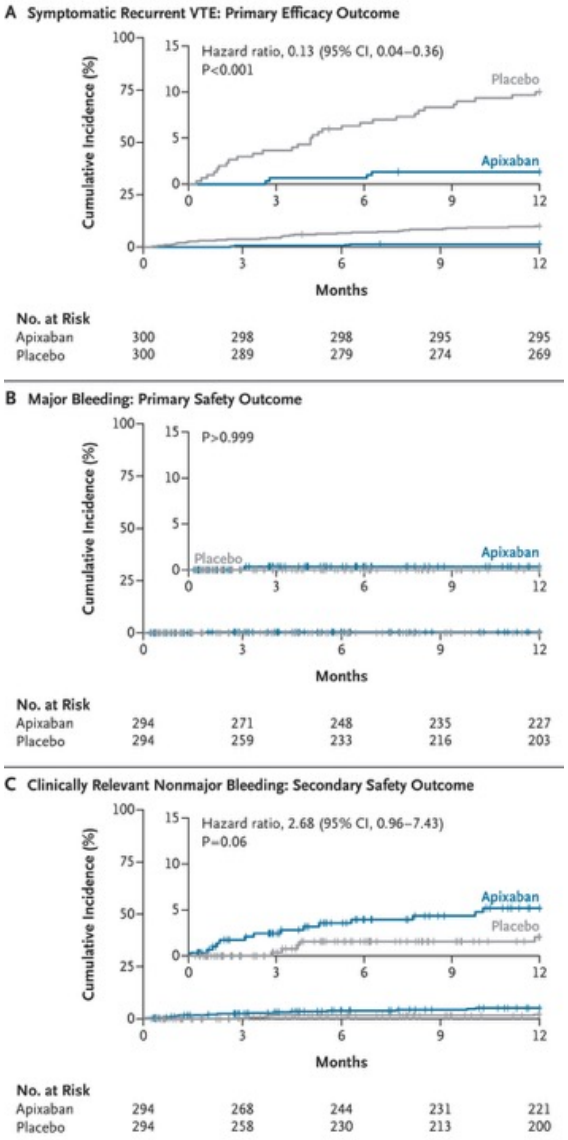
| Characteristic | All Patients (N = 600) | Apixaban (N = 300) | Placebo (N = 300) | Standardized Difference† |
|---|---|---|---|---|
| | | | | % |
| Age — yr | 59.5±15.2 | 59.1±15.2 | 59.9±15.2 | 5.8 |
| Female sex — no. (%) | 342 (57.0) | 176 (58.7) | 166 (55.3) | 6.7 |
| Race — no. (%)‡ | | | | |
| White | 485 (80.8) | 246 (82.0) | 239 (79.7) | 5.9 |
| Black | 70 (11.7) | 33 (11.0) | 37 (12.3) | 4.2 |
| Asian | 5 (0.8) | 4 (1.3) | 1 (0.3) | 11.0 |
| Other | 18 (3.0) | 9 (3.0) | 9 (3.0) | 0 |
| Unknown | 27 (4.5) | 9 (3.0) | 18 (6.0) | 14.5 |
| Hispanic or Latino ethnic group — no. (%)‡ | 55 (9.2) | 26 (8.7) | 29 (9.7) | 3.5 |
| BMI§ | 30.6±6.7 | 30.7±6.8 | 30.4±6.6 | 3.5 |
| Current smoker — no. (%) | 32 (5.3) | 15 (5.0) | 17 (5.7) | 3.0 |
| Coexisting conditions — no. (%)¶ | | | | |
| Previous VTE‖ | 125 (20.8) | 67 (22.3) | 58 (19.3) | 7.4 |
| Diabetes | 71 (11.8) | 40 (13.3) | 31 (10.3) | 9.3 |
| Hypertension | 296 (49.3) | 146 (48.7) | 150 (50.0) | 2.7 |
| Coronary artery disease | 104 (17.3) | 50 (16.7) | 54 (18.0) | 3.5 |
| Peripheral artery disease | 23 (3.8) | 12 (4.0) | 11 (3.7) | 1.7 |
| Stroke or TIA | 31 (5.2) | 17 (5.7) | 14 (4.7) | 4.5 |
| Heart failure | 15 (2.5) | 10 (3.3) | 5 (1.7) | 10.7 |
| Dyslipidemia | 317 (52.8) | 164 (54.7) | 153 (51.0) | 7.4 |
| Carotid occlusive disease | 13 (2.2) | 6 (2.0) | 7 (2.3) | 2.3 |
| Family history of VTE — no. (%) | 154 (25.7) | 78 (26.0) | 76 (25.3) | 1.5 |
| Use of aspirin at ≤81 mg/day — no. (%) | | | | |
| At baseline | 125 (20.8) | 55 (18.3) | 70 (23.3) | 12.3 |
| During follow-up period | 119 (19.8) | 54 (18.0) | 65 (21.7) | 9.2 |

## Characteristics of Venous Thromboembolic (VTE) Events and Risk Factors (Intention-to-Treat Population).

| Characteristic | Total (N = 600) | Apixaban (N = 300) | Placebo (N = 300) | Standardized Difference |
|---|---|---|---|---|
| | | | | % |
| VTE diagnosis for eligibility — no. (%) | | | | |
| Only deep-vein thrombosis | 288 (48.0) | 142 (47.3) | 146 (48.7) | 2.7 |
| Isolated calf deep-vein thrombosis | 119 (19.8) | 48 (16.0) | 71 (23.7) | 19.3 |
| Only pulmonary embolism | 140 (23.3) | 77 (25.7) | 63 (21.0) | 11.1 |
| Right ventricular dysfunction | 80 (13.3) | 38 (12.7) | 42 (14.0) | 3.9 |
| Both pulmonary embolism and deep-vein thrombosis | 172 (28.7) | 81 (27.0) | 91 (30.3) | 7.4 |
| Provoking factors for VTE — no. (%)† | | | | |
| Acute medical illness‡ | 110 (18.3) | 56 (18.7) | 54 (18.0) | 1.7 |
| Surgery | 201 (33.5) | 102 (34.0) | 99 (33.0) | 2.1 |
| Trauma | 115 (19.2) | 62 (20.7) | 53 (17.7) | 7.6 |
| Pregnancy | 11 (1.8) | 7 (2.3) | 4 (1.3) | 7.5 |
| Infection | 99 (16.5) | 45 (15.0) | 54 (18.0) | 8.1 |
| Hormonal contraceptive or replacement therapy | 69 (11.5) | 42 (14.0) | 27 (9.0) | 15.7 |
| Hospitalization ≤3 mo before the VTE event | 56 (9.3) | 25 (8.3) | 31 (10.3) | 6.9 |
| Immobility | 188 (31.3) | 81 (27.0) | 107 (35.7) | 18.8 |
| Blood transfusion§ | 2 (0.3) | 1 (0.3) | 1 (0.3) | 0 |
| Coronavirus disease 2019§ | 49 (8.2) | 23 (7.7) | 26 (8.7) | 3.7 |
| Long-haul travel§ | 100 (16.7) | 46 (15.3) | 54 (18.0) | 7.2 |
| Other factor¶ | 53 (8.8) | 26 (8.7) | 27 (9.0) | 1.2 |
| Enduring risk factors for VTE — no. (%)† | | | | |
| Persistent immobility | 39 (6.5) | 15 (5.0) | 24 (8.0) | 12.2 |
| Obesity: BMI ≥30 | 289 (48.2) | 141 (47.0) | 148 (49.3) | 4.7 |
| Heart failure | 15 (2.5) | 10 (3.3) | 5 (1.7) | 10.7 |
| Chronic lung disease | 134 (22.3) | 78 (26.0) | 56 (18.7) | 17.7 |
| Chronic inflammatory or autoimmune disorder | 313 (52.2) | 152 (50.7) | 161 (53.7) | 6.0 |
| Atherosclerotic cardiovascular disease | 176 (29.3) | 86 (28.7) | 90 (30.0) | 2.9 |
| Chronic kidney disease | 64 (10.7) | 32 (10.7) | 32 (10.7) | 0 |
| Chronic liver disease | 23 (3.8) | 10 (3.3) | 13 (4.3) | 5.2 |
| Median duration of anticoagulant treatment before randomization — mo (IQR) | 6.6 (3.7–35.3) | 7.6 (3.9–39.6) | 5.9 (3.5–32.5) | 6.9 |

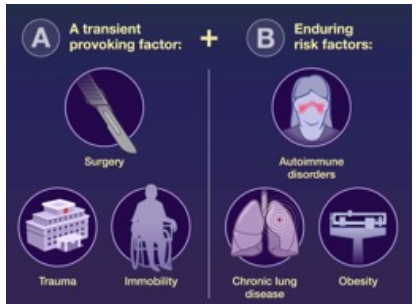
## Prespecified Efficacy and Safety Outcomes (Intention-to-Treat Population).

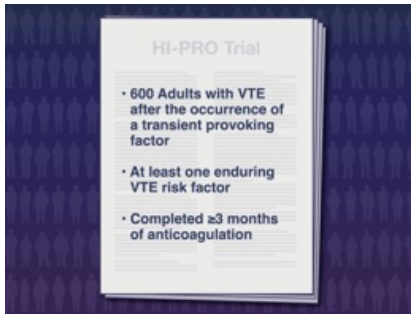
| Outcome | Apixaban | Placebo | Hazard Ratio (95% CI) | P Value |
|---|---|---|---|---|
| | *no./total no. (%)* | | | |
| **Efficacy outcome** | | | | |
| Symptomatic recurrent VTE: primary efficacy outcome | 4/300 (1.3) | 30/300 (10.0) | 0.13 (0.04–0.36) | <0.001 |
| Pulmonary embolism | | | | |
| Any | 0 | 11/300 (3.7) | | |
| Isolated subsegmental | 0 | 1/300 (0.3) | | |
| Deep-vein thrombosis | | | | |
| Any | 4/300 (1.3) | 23/300 (7.7) | | |
| Isolated calf | 2/300 (0.7) | 10/300 (3.3) | | |
| **Secondary efficacy composite outcome** | 2/300 (0.7) | 3/300 (1.0)† | 0.67 (0.11–3.98)‡ | |
| Nonfatal myocardial infarction | 1/300 (0.3) | 0 | | |
| Stroke, TIA, or systemic embolism§ | 1/300 (0.3) | 2/300 (0.7) | | |
| Coronary or peripheral ischemia resulting in revascularization | 0 | 2/300 (0.7) | | |
| **Other outcome** | | | | |
| Additional efficacy composite outcome¶ | 6/300 (2.0) | 32/300 (10.7) | 0.18 (0.07–0.43)‡ | |
| Composite thrombotic outcome‖ | 6/300 (2.0) | 31/300 (10.3) | 0.19 (0.08–0.44)‡ | |
| Death from any cause | 1/300 (0.3) | 3/300 (1.0) | | |
| **Safety outcome** | | | | |
| Major bleeding: primary safety outcome** | 1/294 (0.3) | 0 | NE | >0.999 |
| Clinically relevant nonmajor bleeding: secondary safety outcome** | 14/294 (4.8) | 5/294 (1.7) | 2.68 (0.96–7.43) | 0.06 |

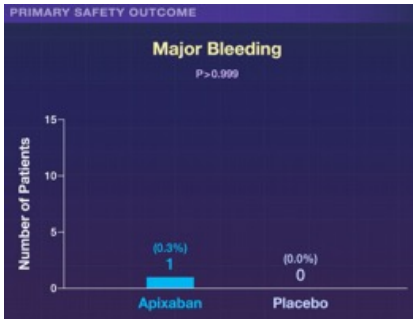


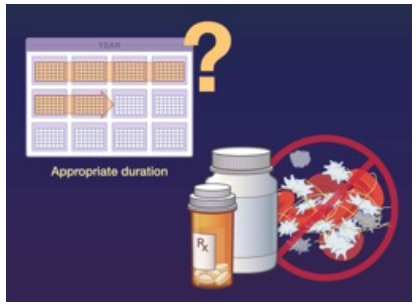

**Symptomatic Recurrent Venous Thromboembolism (VTE), Major Bleeding, and Clinically Relevant Nonmajor Bleeding.**

Shown are Kaplan–Meier curves for the first event of symptomatic recurrent VTE during a 12-month period (the primary efficacy outcome) (Panel A), as well as the first episodes of major bleeding (the primary safety outcome) (Panel B) and clinically relevant nonmajor bleeding (secondary safety outcome) (Panel C) during the period between administration of the first dose of apixaban or placebo and 96 hours after administration of the last dose. In each panel, the inset shows the same data on an enlarged y axis.

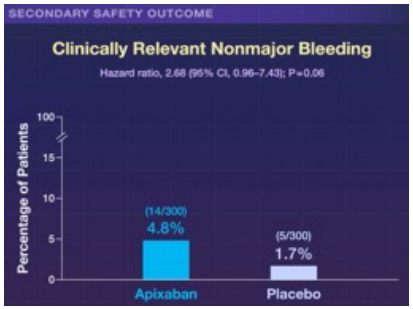

A
A transient provoking factor:
+
B
Enduring risk factors:
Surgery
Autoimmune disorders
Trauma
Immobility
Chronic lung disease
Obesity


HI-PRO Trial
• 600 Adults with VTE after the occurrence of a transient provoking factor
• At least one enduring VTE risk factor
• Completed ≥3 months of anticoagulation

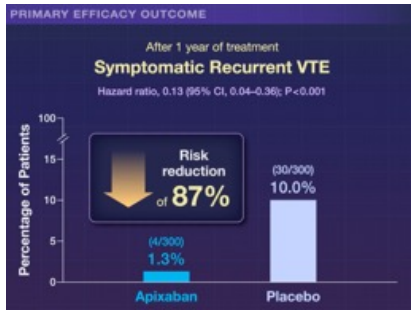

PRIMARY SAFETY OUTCOME
Major Bleeding
P>0.999
Number of Patients
15
10
5
0
(0.3%)
1
(0.0%)
0
Apixaban
Placebo

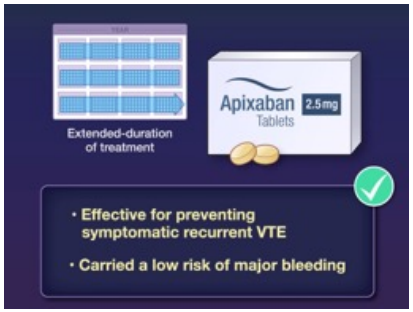

YEAR
Appropriate duration
Rx


Apixaban
N=300
Placebo
N=300
Apixaban 2.5mg Tablets
Placebo 0.0mg Tablets
2.5 mg twice daily

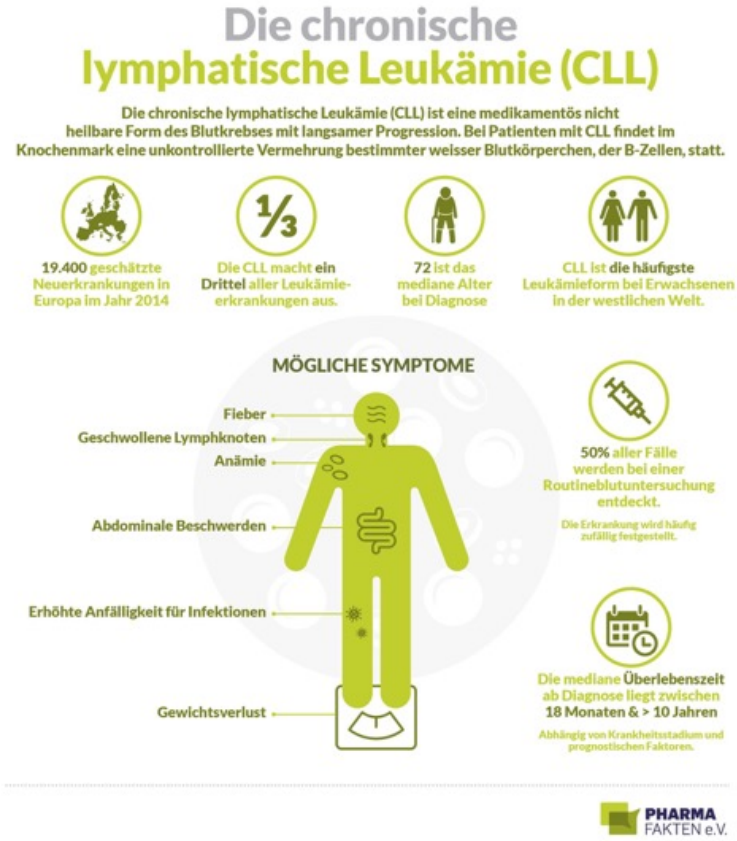

SECONDARY SAFETY OUTCOME
Clinically Relevant Nonmajor Bleeding
Hazard ratio, 2.68 (95% CI, 0.96–7.43); P=0.06
Percentage of Patients
100
15
10
5
0
(14/300)
4.8%
(5/300)
1.7%
Apixaban
Placebo

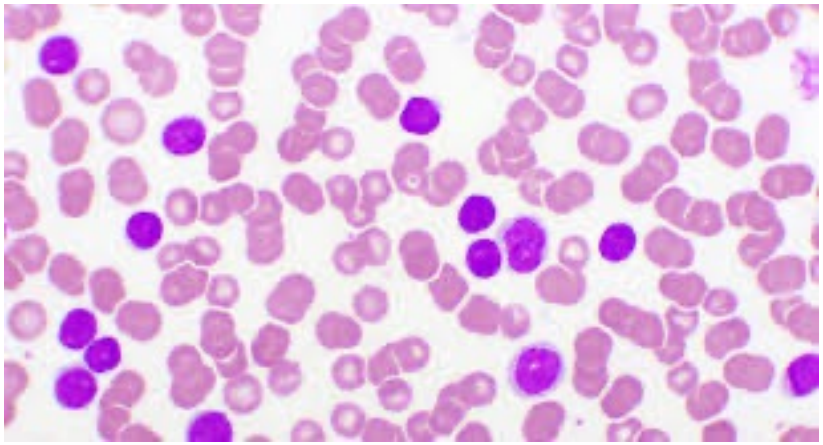

Efficacy and Safety
In the prevention of recurrent VTE
Extended-duration
Apixaban 2.5mg Tablets


PRIMARY EFFICACY OUTCOME
After 1 year of treatment
Symptomatic Recurrent VTE
Hazard ratio, 0.13 (95% CI, 0.04–0.36); P<0.001
Percentage of Patients
100
15
10
5
0
Risk reduction of 87%
(4/300)
1.3%
(30/300)
10.0%
Apixaban
Placebo


YEAR
Extended-duration of treatment
Apixaban 2.5mg Tablets
• Effective for preventing symptomatic recurrent VTE
• Carried a low risk of major bleeding

Die Chronische Lymphatische Leukämie (CLL) ist eine Form von Blutkrebs, bei der es zu einer unkontrollierten Vermehrung von B-Lymphozyten (einer Art weißer Blutkörperchen) kommt. Diese bösartig veränderten Zellen finden sich vor allem im Knochenmark, Blut und Lymphsystem, was zu Symptomen wie Lymphknotenschwellungen, Abgeschlagenheit und Infektanfälligkeit führen kann. Die CLL schreitet in der Regel langsam voran und betrifft hauptsächlich ältere Menschen.

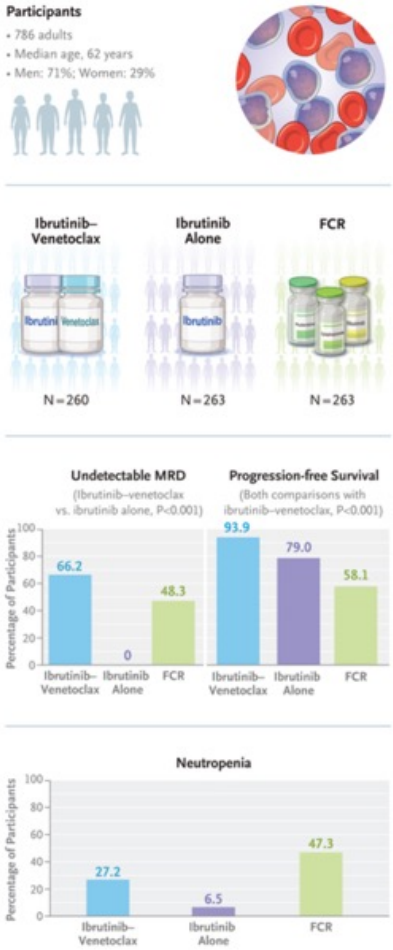


# Measurable Residual Disease–Guided Therapy for Chronic Lymphocytic Leukemia

An interim analysis of progression-free survival in this trial showed that ibrutinib–venetoclax was superior to fludarabine–cyclophosphamide–rituximab (FCR) among patients with chronic lymphocytic leukemia (CLL). Whether ibrutinib–venetoclax is more effective than ibrutinib alone is unclear.

In this phase 3, multicenter, open-label trial, we randomly assigned patients with CLL to receive ibrutinib–venetoclax, ibrutinib alone, or FCR. The primary end points were undetectable measurable residual disease (MRD) in bone marrow within 2 years in the ibrutinib–venetoclax group as compared with the ibrutinib-alone group and progression-free survival in the ibrutinib–venetoclax group as compared with the FCR group. A powered secondary end point was progression-free survival in the ibrutinib–venetoclax group as compared with the ibrutinib-alone group. Other secondary end points included overall survival.



Chronic lymphocytic leukemia (CLL) affects approximately 4.6 per 100,000 persons.[1] In patients with CLL, malignant B cells proliferate autonomously through B-cell receptor (BCR) signaling that is mediated by Bruton's tyrosine kinase (BTK) and also do not undergo apoptosis owing in part to overexpression of the antiapoptotic protein B-cell lymphoma 2 (BCL2). Ibrutinib, an oral BTK inhibitor, blocks BCR signaling and thus reduces CLL-cell proliferation, migration, and adhesion. Venetoclax, an oral small-molecule inhibitor of BCL2, leads to CLL-cell apoptosis.

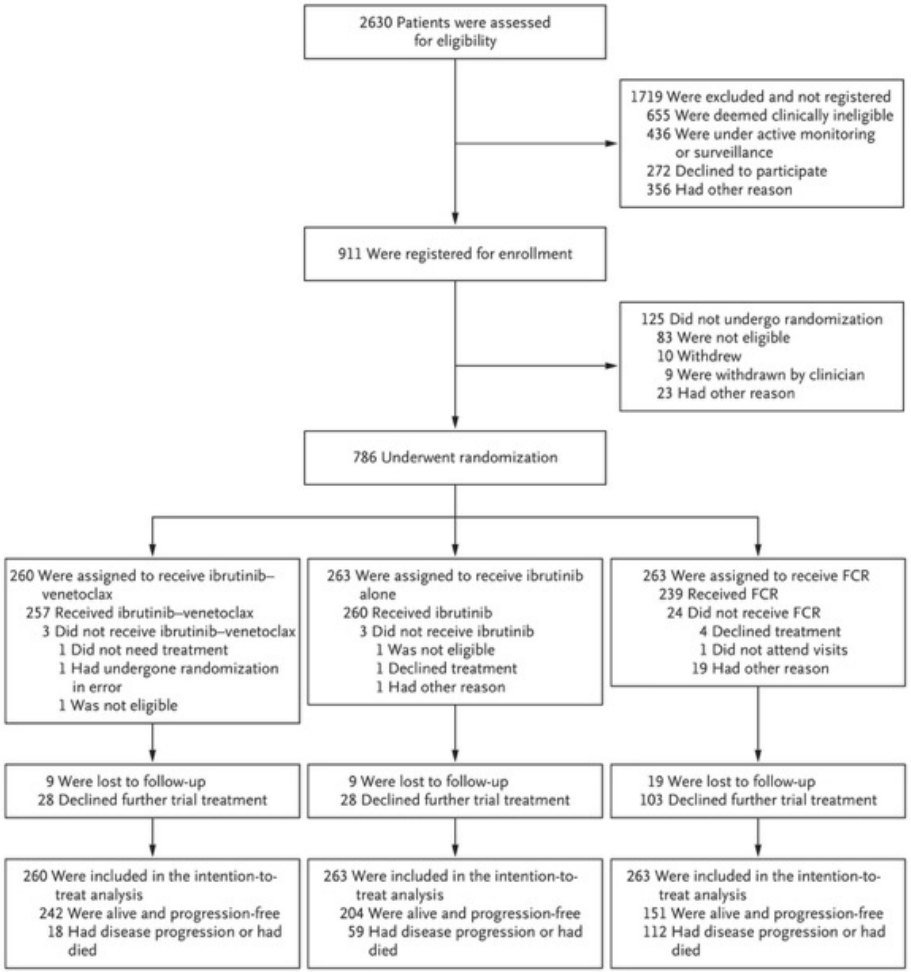
The FLAIR trial involving patients with previously untreated CLL has been adapted to include MRD-guided ibrutinib–venetoclax therapy, MRD-guided ibrutinib monotherapy, and fludarabine–cyclophosphamide–rituximab (FCR) therapy. An interim analysis of progression-free survival in the trial showed that ibrutinib–venetoclax was superior to FCR. Here, we present the results of a planned analysis comparing MRD-guided ibrutinib–venetoclax with ibrutinib alone and FCR with extended follow-up.

**Randomization and Procedures**

Participants were randomly assigned (in a 1:1:1 ratio) to receive ibrutinib–venetoclax, ibrutinib alone, or FCR. Randomization was performed with the use of a computer-generated minimization algorithm with a random element.

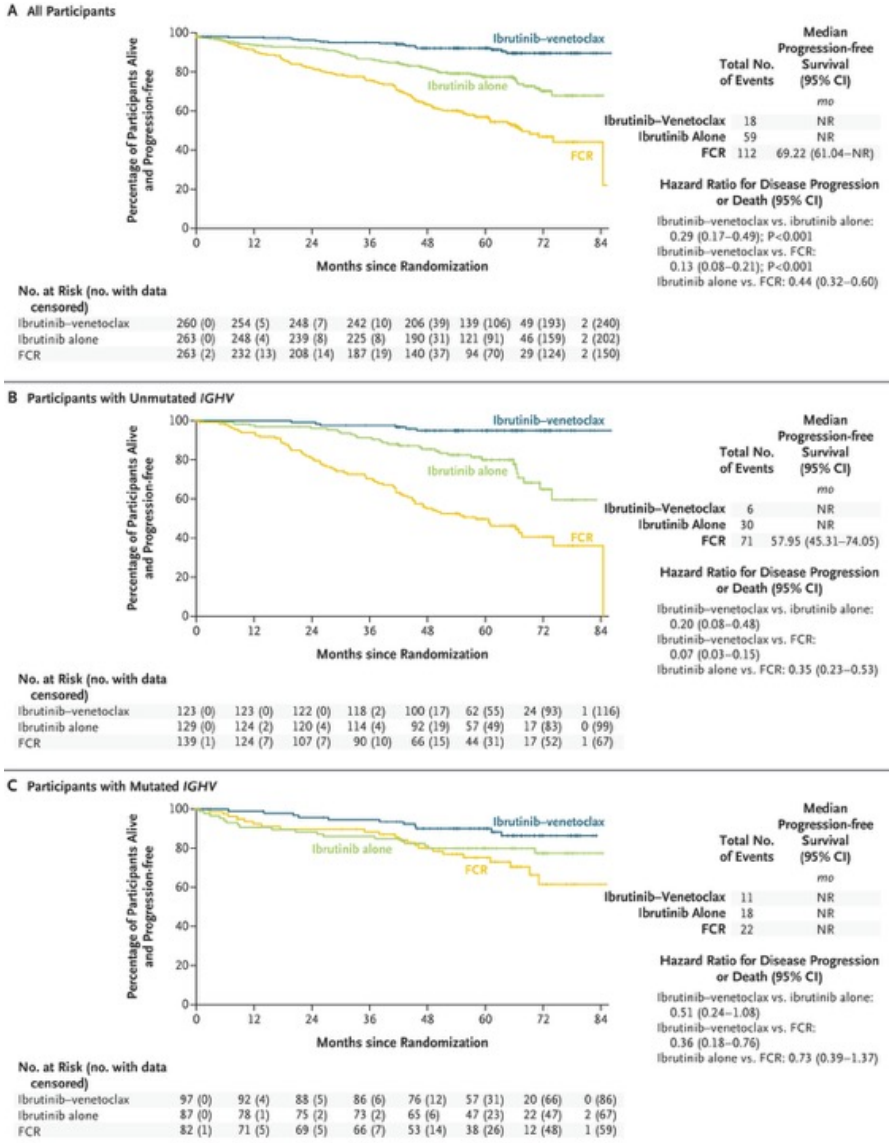
## Assessments and End Points

The primary end point that was assessed in the ibrutinib–venetoclax group as compared with the ibrutinib-alone group was undetectable MRD in bone marrow within 2 years after randomization. The primary end point that was assessed in the ibrutinib–venetoclax group as compared with the FCR group was progression-free survival. A powered secondary end point that was assessed in the ibrutinib–venetoclax group as compared with the ibrutinib-alone group was progression-free survival. Other secondary end points were overall survival, undetectable MRD in bone marrow and peripheral blood 9 months after randomization and at each follow-up assessment (performed every 6 months from 1 year through 6 years after randomization).



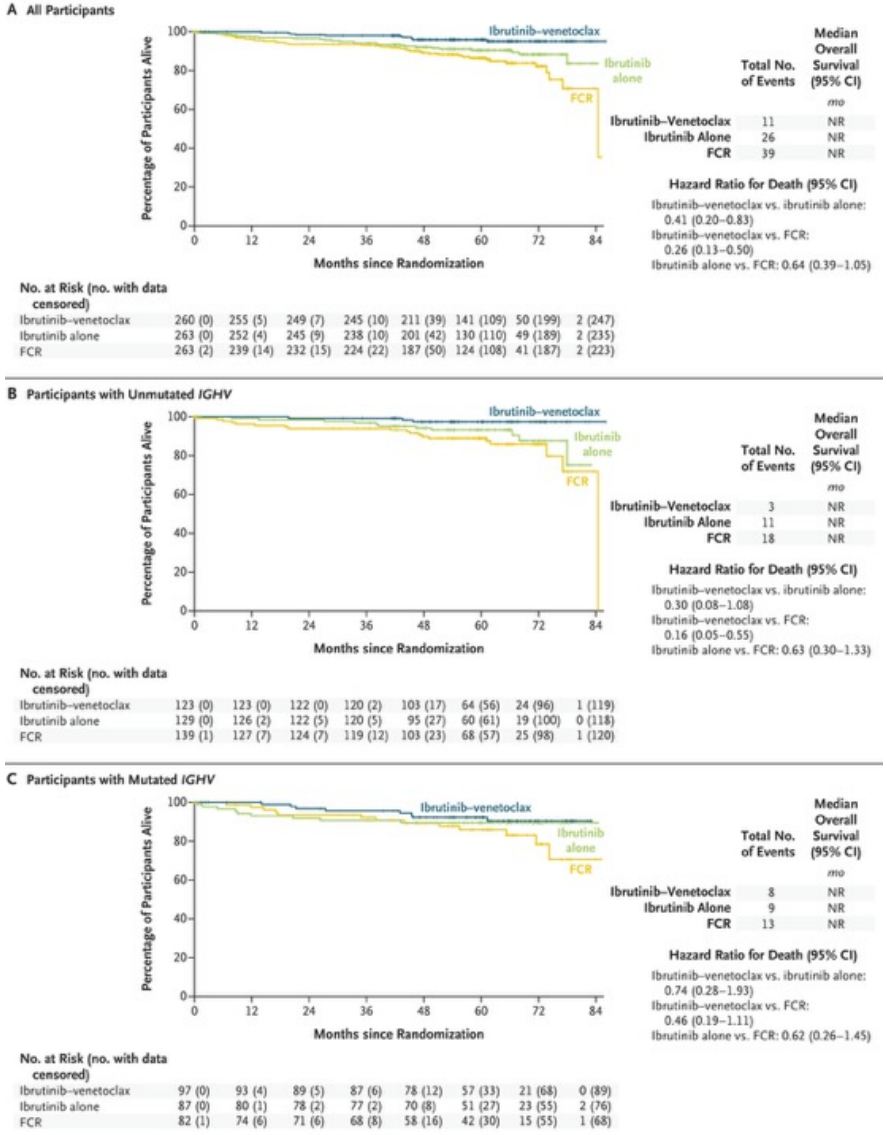

**Characteristics of the Participants at Baseline (Intention-to-Treat Population).**

| Characteristic | Ibrutinib–Venetoclax (N = 260) | Ibrutinib Alone (N = 263) | FCR (N = 263) | |
|---|---|---|---|---|
| Age | | | | |
| Median (IQR) — yr | 62 (55–67) | 62 (56–67) | 62 (57–67) | |
| Distribution — no. (%) | | | | |
| ≤65 yr | 179 (68.8) | 179 (68.1) | 181 (68.8) | 539 (68.6) |
| >65 yr | 81 (31.2) | 84 (31.9) | 82 (31.2) | 247 (31.4) |
| Sex — no. (%) | | | | |
| Male | 186 (71.5) | 186 (70.7) | 187 (71.1) | 559 (71.1) |
| Female | 74 (28.5) | 77 (29.3) | 76 (28.9) | 227 (28.9) |
| Binet stage — no. (%)† | | | | |
| Progressive A or B | 154 (59.2) | 153 (58.2) | 154 (58.6) | 461 (58.7) |
| C | 106 (40.8) | 110 (41.8) | 109 (41.4) | 325 (41.3) |
| Race — no. (%)‡ | | | | |
| White | 235 (90.4) | 241 (91.6) | 240 (91.3) | 716 (91.1) |
| Asian | 5 (1.9) | 8 (3.0) | 5 (1.9) | 18 (2.3) |
| Black | 7 (2.7) | 4 (1.5) | 3 (1.1) | 14 (1.8) |
| Other | 3 (1.2) | 1 (0.4) | 1 (0.4) | 5 (0.6) |
| Not available | 10 (3.8) | 9 (3.4) | 14 (5.3) | 33 (4.2) |
| WHO performance-status score — no. (%)§ | | | | |
| 0 | 181 (69.6) | 187 (71.1) | 181 (68.8) | 549 (69.8) |
| 1 | 69 (26.5) | 70 (26.6) | 69 (26.2) | 208 (26.5) |
| 2 | 8 (3.1) | 5 (1.9) | 8 (3.0) | 21 (2.7) |
| Missing data | 2 (0.8) | 1 (0.4) | 5 (1.9) | 8 (1.0) |
| B symptoms — no. (%)¶ | | | | |
| Yes | 128 (49.2) | 126 (47.9) | 121 (46.0) | 375 (47.7) |
| No | 130 (50.0) | 136 (51.7) | 133 (50.6) | 399 (50.8) |
| Missing data | 2 (0.8) | 1 (0.4) | 9 (3.4) | 12 (1.5) |
| Median creatinine clearance (range) — ml/min‖ | 83.0 (40.0–231) | 80.1 (41.0–260) | 79.0 (37.0–247) | 81.0 (37.0–260) |
| Median $\beta_2$-microglobulin concentration (range) — mg/liter** | 4.00 (1.90–14.3) | 4.10 (1.70–17.9) | 4.00 (1.70–13.1) | 4.00 (1.70–17.9) |
| Duration of CLL — mo†† | | | | |
| Mean | 37.9±44.6 | 36.2±37.9 | 33.4±33.9 | 35.9±39.2 |
| Median (range) | 23.7 (0.00–263) | 27.5 (0.33–241) | 21.3 (0.00–162) | 24.9 (0.00–263) |
| *IGHV* mutation status — no. (%) | | | | |
| Mutated | 97 (37.3) | 87 (33.1) | 82 (31.2) | 266 (33.8) |
| Unmutated | 123 (47.3) | 129 (49.0) | 139 (52.9) | 391 (49.7) |
| BCR subset 2 mutated | 11 (4.2) | 15 (5.7) | 6 (2.3) | 32 (4.1) |
| BCR subset 2 unmutated | 5 (1.9) | 8 (3.0) | 8 (3.0) | 21 (2.7) |
| Not available | 24 (9.2) | 24 (9.1) | 28 (10.6) | 76 (9.7) |
| Hierarchical genetic abnormalities — no. (%) | | | | |
| *TP53* deletion‡‡ | 1 (0.4) | 0 | 0 | 1 (0.1) |
| *ATM* deletion | 45 (17.3) | 36 (13.7) | 50 (19.0) | 131 (16.7) |
| Trisomy 12 | 57 (21.9) | 45 (17.1) | 29 (11.0) | 131 (16.7) |
| Normal karyotype | 52 (20.0) | 64 (24.3) | 69 (26.2) | 185 (23.5) |
| 13q deletion | 89 (34.2) | 106 (40.3) | 100 (38.0) | 295 (37.5) |
| Undetermined | 16 (6.2) | 12 (4.6) | 15 (5.7) | 43 (5.5) |




**Progression-free Survival.**

Shown are progression-free survival estimates among all participants (Panel A), participants with unmutated *IGHV* (Panel B), and participants with mutated *IGHV* (Panel C). Tick marks indicate censored data. NR denotes not reached.

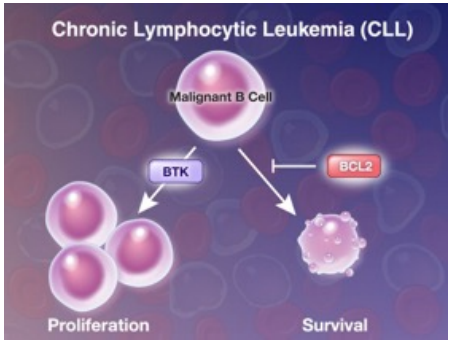



**Overall Survival.**

Shown are overall survival estimates among all participants (Panel A), participants with unmutated *IGHV* (Panel B), and participants with mutated *IGHV* (Panel C). Tick marks indicate censored data.

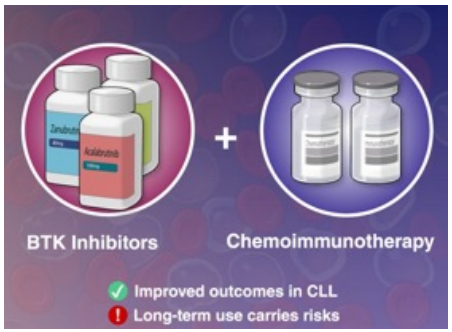
## Adverse Events According to Maximum Grade (Safety Population).

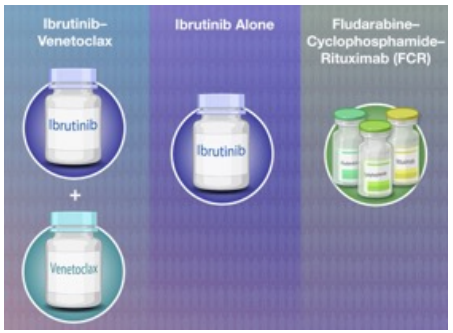
| Event | Ibrutinib–Venetoclax (N=257) | | | | Ibrutinib Alone (N=260) | | | | FCR (N=239) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Grade 1 or 2 | Grade 3 | Grade 4 | Grade 5 | Grade 1 or 2 | Grade 3 | Grade 4 | Grade 5 | Grade 1 or 2 | Grade 3 | Grade 4 | Grade 5 |
| | *number of participants (percent)* | | | | | | | | | | | |
| Abdominal pain or bloating | 37 (14.4) | 0 | 0 | 0 | 15 (5.8) | 1 (0.4) | 0 | 0 | 21 (8.8) | 0 | 0 | 0 |
| Anemia | 61 (23.7) | 16 (6.2) | 2 (0.8) | 0 | 52 (20) | 11 (4.2) | 1 (0.4) | 0 | 50 (20.9) | 33 (13.8) | 5 (2.1) | 0 |
| Arthralgia or arthritis | 56 (21.8) | 1 (0.4) | 0 | 0 | 49 (18.8) | 2 (0.8) | 0 | 0 | 10 (4.2) | 0 | 0 | 0 |
| Bruising or bleeding | 85 (33.1) | 0 | 0 | 0 | 78 (30) | 1 (0.4) | 0 | 0 | 4 (1.7) | 0 | 0 | 0 |
| Constipation | 29 (11.3) | 2 (0.8) | 0 | 0 | 23 (8.8) | 0 | 0 | 0 | 60 (25.1) | 0 | 0 | 0 |
| Cough | 23 (8.9) | 0 | 0 | 0 | 25 (9.6) | 0 | 0 | 0 | 47 (19.7) | 4 (1.7) | 0 | 0 |
| Diarrhea | 114 (44.4) | 3 (1.2) | 0 | 0 | 66 (25.4) | 1 (0.4) | 0 | 0 | 46 (19.2) | 6 (2.5) | 0 | 0 |
| Dyspepsia | 33 (12.8) | 0 | 0 | 0 | 30 (11.5) | 0 | 0 | 0 | 9 (3.8) | 0 | 0 | 0 |
| Fatigue | 97 (37.7) | 1 (0.4) | 0 | 0 | 89 (34.2) | 2 (0.8) | 0 | 0 | 108 (45.2) | 9 (3.8) | 0 | 0 |
| Fever | 23 (8.9) | 2 (0.8) | 0 | 0 | 22 (8.5) | 2 (0.8) | 0 | 0 | 59 (24.7) | 18 (7.5) | 0 | 0 |
| Headache | 39 (15.2) | 2 (0.8) | 0 | 0 | 40 (15.4) | 2 (0.8) | 0 | 0 | 31 (13) | 1 (0.4) | 0 | 0 |
| Infusion-related reaction | 1 (0.4) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 65 (27.2) | 2 (0.8) | 1 (0.4) | 0 |
| Mouth ulcers | 38 (14.8) | 1 (0.4) | 0 | 0 | 29 (11.2) | 1 (0.4) | 0 | 0 | 11 (4.6) | 0 | 0 | 0 |
| Nausea | 93 (36.2) | 3 (1.2) | 0 | 0 | 40 (15.4) | 0 | 0 | 0 | 138 (57.7) | 1 (0.4) | 0 | 0 |
| Other | 65 (25.3) | 16 (6.2) | 0 | 0 | 81 (31.2) | 13 (5) | 0 | 0 | 31 (13) | 9 (3.8) | 1 (0.4) | 1 (0.4) |
| Platelet count decreased | 55 (21.4) | 8 (3.1) | 5 (1.9) | 0 | 44 (16.9) | 1 (0.4) | 1 (0.4) | 0 | 65 (27.2) | 16 (6.7) | 8 (3.3) | 0 |
| Rash | 82 (31.9) | 5 (1.9) | 0 | 0 | 74 (28.5) | 8 (3.1) | 0 | 0 | 67 (28.0) | 6 (2.5) | 0 | 0 |
| Upper respiratory infection | 22 (8.6) | 5 (1.9) | 0 | 0 | 31 (11.9) | 2 (0.8) | 0 | 0 | 26 (10.9) | 8 (3.3) | 0 | 0 |
| Vomiting | 35 (13.6) | 2 (0.8) | 0 | 0 | 17 (6.5) | 0 | 0 | 0 | 66 (27.6) | 5 (2.1) | 0 | 0 |
| White-cell count decreased | 31 (12.1) | 38 (14.8) | 32 (12.5) | 0 | 12 (4.6) | 4 (1.5) | 13 (5) | 0 | 28 (11.7) | 53 (22.2) | 60 (25.1) | 0 |

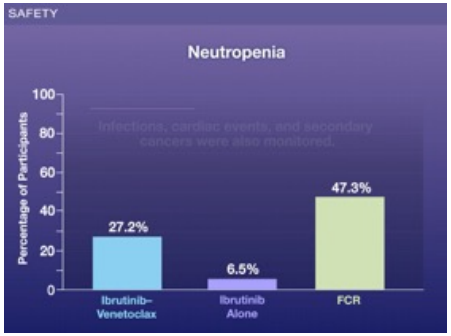

Chronic Lymphocytic Leukemia (CLL)
Malignant B Cell
BTK
BCL2
Proliferation
Survival


FLAIR TRIAL
• Phase 3
• Multicenter
• Open-label
• 786 Adults
• Previously untreated CLL

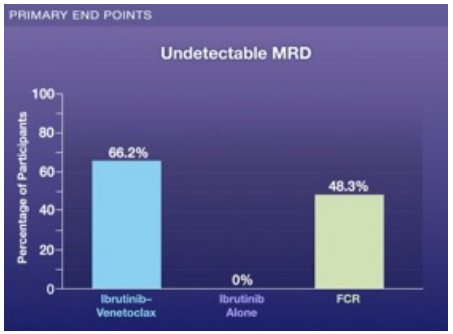

PRIMARY END POINTS
Progression-free Survival at 5 Years
Percentage of Participants
100
80
60
40
20
0
93.9%
79.0%
58.1%
Ibrutinib–Venetoclax
Ibrutinib Alone
FCR


BTK Inhibitors
Chemoimmunotherapy
Improved outcomes in CLL
Long-term use carries risks


Ibrutinib–Venetoclax
Ibrutinib Alone
Fludarabine–Cyclophosphamide–Rituximab (FCR)
Ibrutinib
Venetoclax

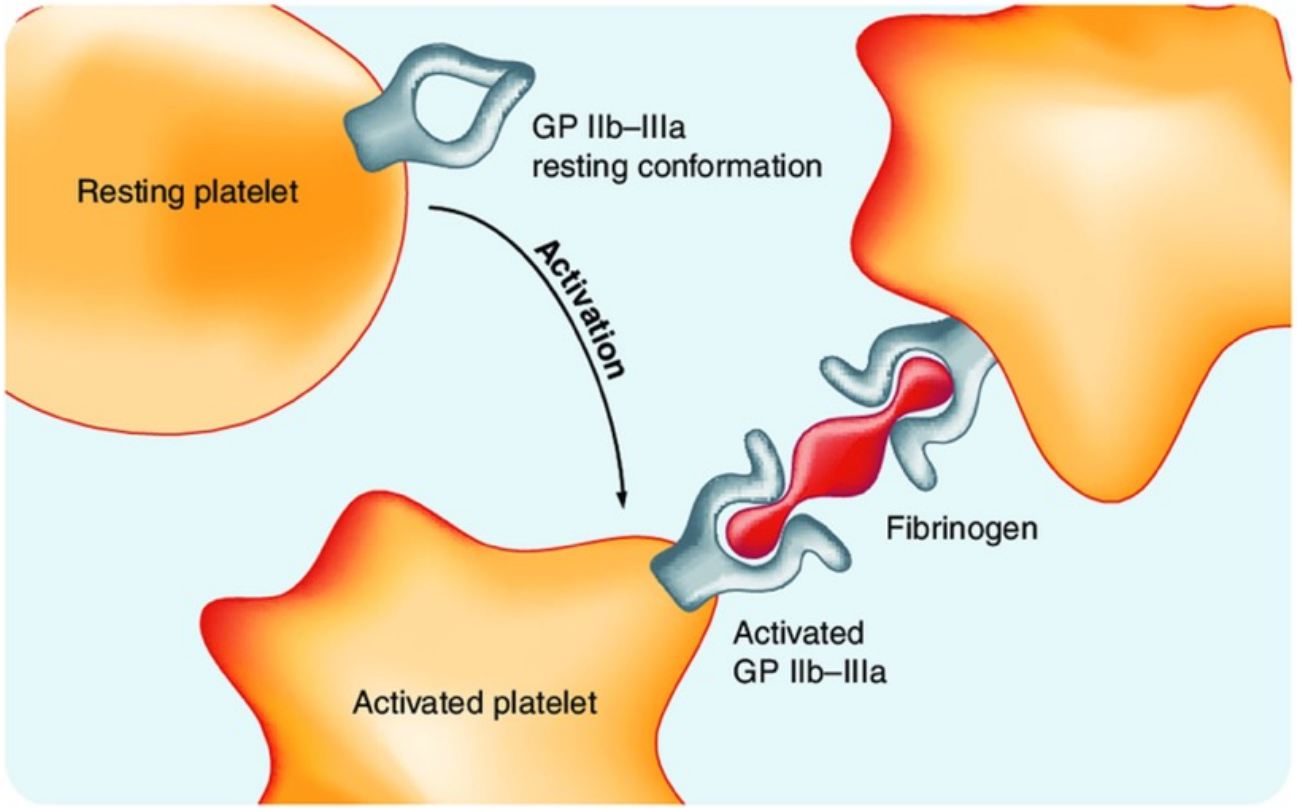

SAFETY
Neutropenia
Percentage of Participants
100
80
60
40
20
0
27.2%
6.5%
47.3%
Ibrutinib–Venetoclax
Ibrutinib Alone
FCR


Response-Guided Therapy
Ibrutinib
Venetoclax
Outcomes

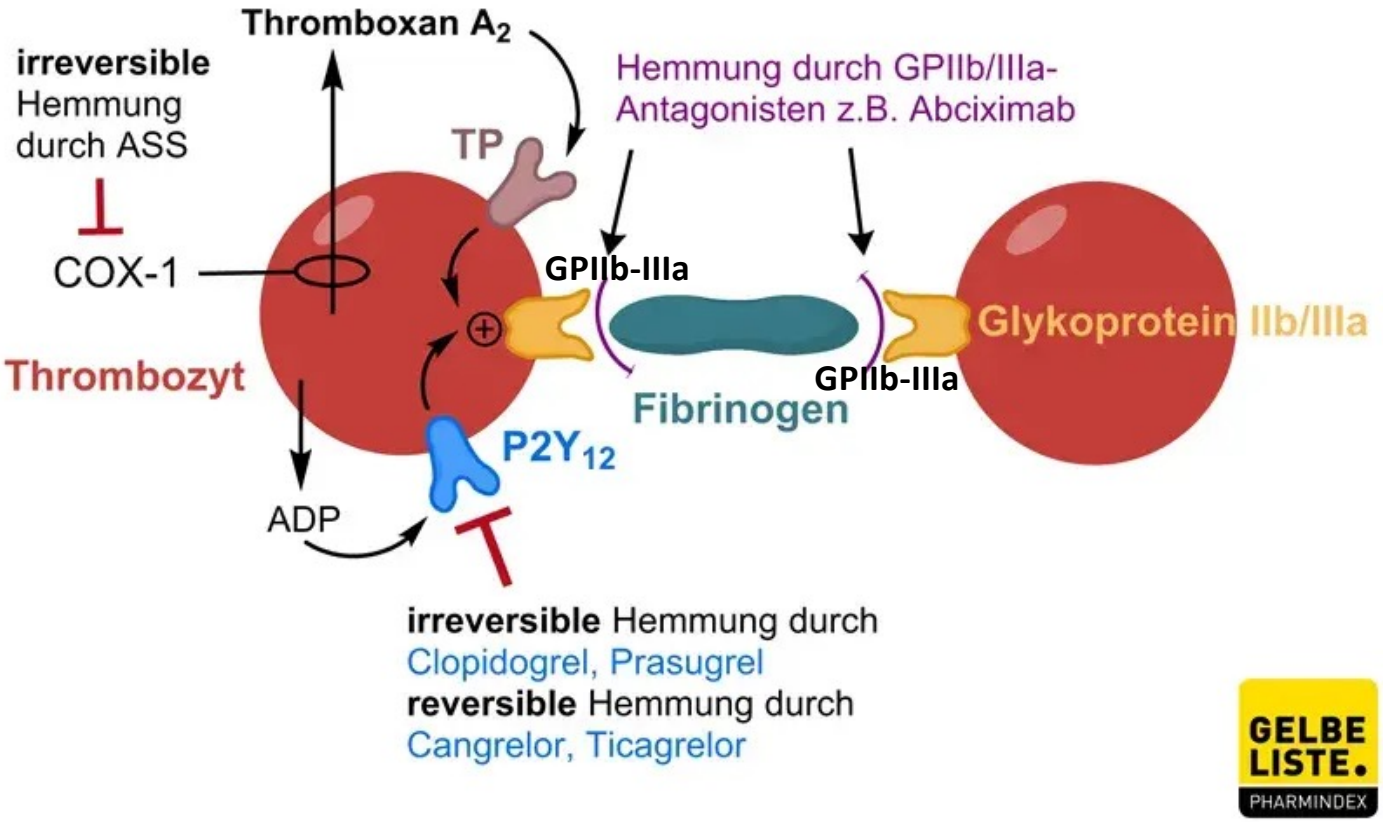

PRIMARY END POINTS
Undetectable MRD
Percentage of Participants
100
80
60
40
20
0
66.2%
0%
48.3%
Ibrutinib–Venetoclax
Ibrutinib Alone
FCR


Ibrutinib
Venetoclax
Improved progression-free survival in patients with previously untreated CLL
Suggested overall survival benefit

GP IIb/IIIa ist ein wichtiger Rezeptor auf Blutplättchen, der bei der Blutstillung und der Bildung von Blutgerinnseln eine zentrale Rolle spielt. Wenn ein Blutgefäß verletzt wird, ermöglicht der aktivierte GP IIb/IIIa-Rezeptor den Blutplättchen, sich über Brückenmoleküle wie Fibrinogen und den von-Willebrand-Faktor aneinander zu binden (Aggregation). Dies führt zur Bildung eines Thrombus (Blutgerinnsels), der die Blutungsstelle verschließt.



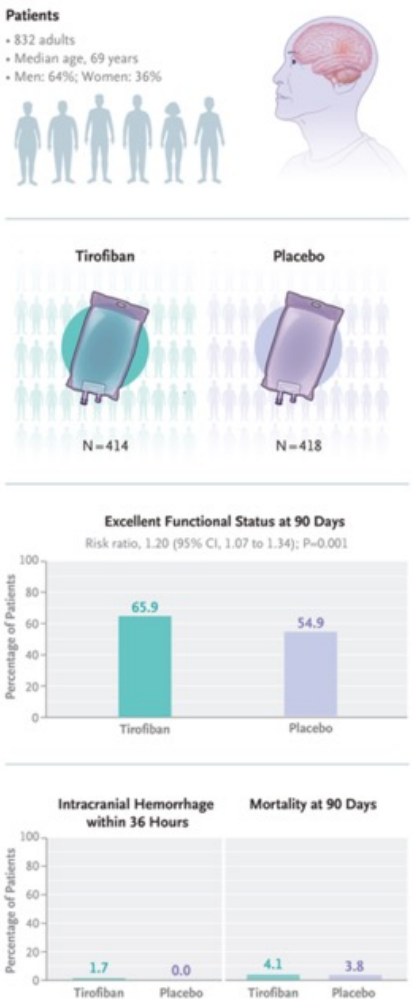
Tirofiban hemmt GPIIb-IIIa, wie abciximab. GPIIb-IIIa ist auch für Glanzmanns Throbasthenie verantwortlcih.



# Early Tirofiban Infusion after Intravenous Thrombolysis for Stroke

Intravenous thrombolysis remains a standard treatment for acute ischemic stroke within 4.5 hours after onset. Vascular reocclusion may occur after intravenous thrombolysis and may be preventable with an antiplatelet agent within the first 24 hours after thrombolysis. Tirofiban, a platelet glycoprotein IIb–IIIa receptor antagonist, has reduced macrovascular reocclusion in experimental models.

In this phase 3, multicenter, double-blind, randomized, placebo-controlled trial conducted at 38 centers in China, we assigned patients with acute ischemic noncardioembolic stroke who presented within 4.5 hours after stroke onset and who were not eligible for thrombectomy to receive a 24-hour intravenous infusion of tirofiban or placebo within 60 minutes after intravenous thrombolysis. The primary efficacy outcome was an excellent functional outcome, defined as a score of 0 to 1 on the modified Rankin scale, at 90 days. The safety outcomes were symptomatic intracranial hemorrhage within 36 hours and death at 90 days.



Acute ischemic stroke is the leading cause of death in China and among the leading causes of death worldwide. Current guidelines recommend intravenous thrombolysis to treat acute ischemic stroke within 4.5 hours after symptom onset (or the last time a patient was known to be well). However, only 50% of patients have an excellent functional outcome, defined as a score of 0 (no symptoms) or 1 (an ability to carry out all usual activities despite some symptoms) on the modified Rankin scale.

Tirofiban, an antagonist of platelet glycoprotein IIb–IIIa receptor, can reduce macrovascular reocclusion, prevent microvascular thrombosis, and improve cerebral blood flow in experimental models. Its rapid onset makes it well suited for use after intravenous thrombolysis for the prevention of potential reocclusion. Previous studies of tirofiban as an adjunct treatment in acute ischemic stroke have been inconclusive because they were limited by a small sample size and single-center or observational designs.

We performed the ASSET-IT (Advancing Stroke Safety and Efficacy through Early Tirofiban Administration after Intravenous Thrombolysis) trial to assess the efficacy and safety of early tirofiban administration after intravenous thrombolysis. Because of differences in thrombus composition and expected treatment response, we excluded patients with cardioembolic stroke. Fibrin-rich clots, typical in cardioembolic stroke, may respond less favorably to tirofiban than platelet-rich thrombi observed in large-artery atherosclerosis. This approach also aligns with previous trials of tirofiban that focused on noncardioembolic stroke.

**Patients**

Adult patients (≥18 years of age) with acute ischemic noncardioembolic stroke who had received intravenous thrombolysis (alteplase or tenecteplase) within 4.5 hours after stroke onset (or the last time a patient was known to be well) were eligible for enrollment. Among the patients, 830 were Han Chinese and 2 were Hui. All the patients underwent randomization within 55 minutes after completing intravenous thrombolysis and received tirofiban or placebo within 5 minutes after randomization.

**Interventions**

All the patients received either tirofiban or placebo intravenously within 5 minutes after randomization. In the intervention group, tirofiban was administered as a continuous infusion of 0.4 μg per kilogram of body weight for 30 minutes, followed by a maintenance dose of 0.1 μg per kilogram per minute for 23.5 hours. Placebo was administered intravenously in a volume and infusion rate identical to those for the tirofiban regimen. At the 24th hour, the intravenous infusions were discontinued. After that, all the patients were treated according to current stroke-management guidelines.

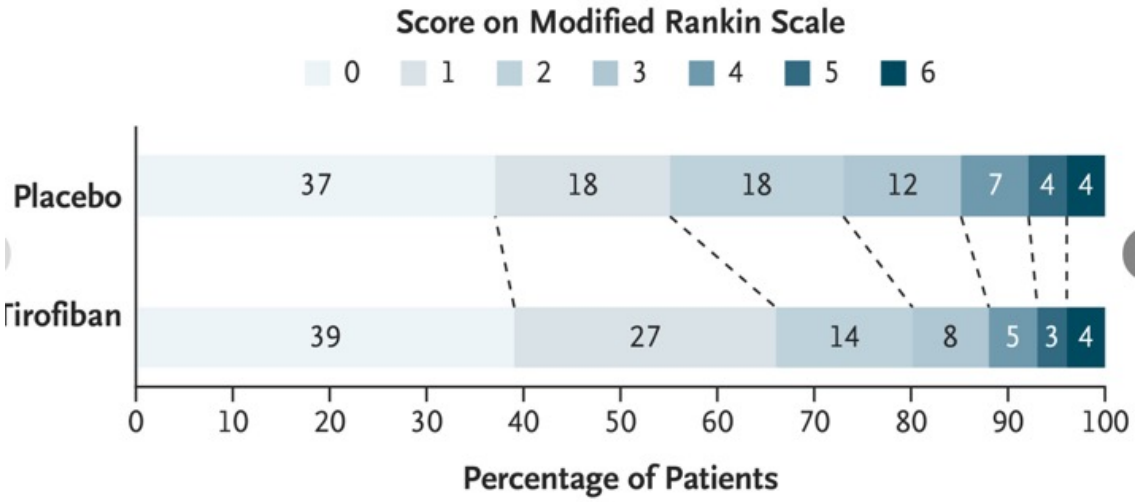
**Outcomes**

The primary outcome was the percentage of patients with excellent functional status, which was defined as score of 0 or 1 on the modified Rankin scale, at 90 days.

| Characteristic | Tirofiban (N=414) | Placebo (N=418) |
|---|---|---|
| Median age (IQR) — yr | 69 (59–76) | 69 (59–76) |
| Male sex — no. (%) | 260 (62.8) | 271 (64.8) |
| Score of 1 on modified Rankin scale before stroke onset — no. (%)† | 28 (6.8) | 16 (3.8) |
| Median NIHSS score (IQR)‡ | 6 (5–9) | 6 (5–9) |
| Median NCCT ASPECTS score (IQR)§ | 10 (9–10) | 10 (9–10) |
| Type of baseline parenchymal imaging — no. (%) | | |
| Computed tomography | 317 (76.6) | 304 (72.7) |
| Magnetic resonance imaging | 97 (23.4) | 114 (27.3) |
| Type of baseline vascular imaging — no. (%) | | |
| Computed tomographic angiography | 79 (19.1) | 85 (20.3) |
| Magnetic resonance angiography | 57 (13.8) | 72 (17.2) |
| Medical history — no. (%) | | |
| Previous stroke or transient ischemic attack | 105 (25.4) | 125 (29.9) |
| Diabetes mellitus | 91 (22.0) | 100 (23.9) |
| Hypertension | 342 (82.6) | 336 (80.4) |
| Ischemic heart disease | 49 (11.8) | 41 (9.8) |
| Hyperlipidemia | 51 (12.3) | 58 (13.9) |
| Cause of stroke — no. (%)¶ | | |
| Large-artery atherosclerosis | 247 (59.7) | 237 (56.7) |
| Small-artery occlusion | 139 (33.6) | 151 (36.1) |
| Undetermined | 27 (6.5) | 26 (6.2) |
| Confirmed large- or medium-vessel occlusion — no./total no. (%)‖ | | |
| First segment of the middle cerebral artery | 24/136 (17.6) | 17/157 (10.8) |
| Second segment of the middle cerebral artery | 12/136 (8.8) | 14/157 (8.9) |
| Internal carotid artery | 7/136 (5.1) | 9/157 (5.7) |
| Basilar artery | 1/136 (0.7) | 3/157 (1.9) |
| Vertebral artery | 5/136 (3.7) | 2/157 (1.3) |
| Anterior cerebral artery | 3/136 (2.2) | 5/157 (3.2) |
| Posterior cerebral artery | 4/136 (2.9) | 13/157 (8.3) |
| Smoking status — no. (%) | | |
| Current smoker | 82 (19.8) | 98 (23.4) |
| Former smoker | 6 (1.4) | 8 (1.9) |
| Intravenous thrombolysis | | |
| Drug administered — no. (%) | | |
| Alteplase | 314 (75.8) | 308 (73.7) |
| Tenecteplase | 100 (24.2) | 110 (26.3) |
| Median duration (IQR) — min | | |
| From stroke onset to thrombolysis | 155 (111–206) | 170 (129–220) |
| From thrombolysis completion to randomization | 29 (12–47) | 30 (13–47) |
| From thrombolysis completion to administration of tirofiban or placebo | 44 (27–55) | 44 (26–54) |
| Type if antiplatelet therapy started 24 hr after thrombolysis — no. (%) | | |
| Monotherapy | 113 (27.3) | 121 (29.0) |
| Dual therapy | 267 (64.5) | 275 (65.8) |

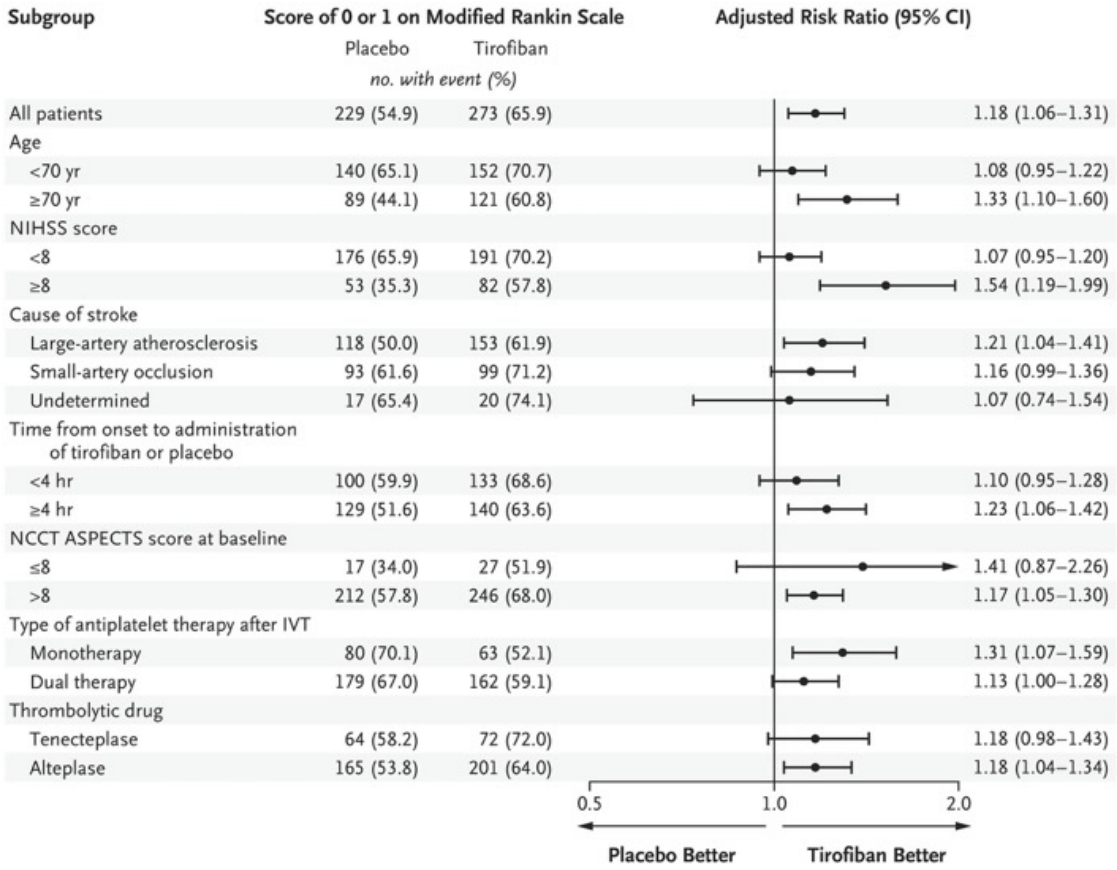
## Primary and Secondary Outcomes.

| Outcome | Tirofiban (N=414) | Placebo (N=418) | Effect Size (95% CI)☆ |
|---|---|---|---|
| **Primary outcome** | | | |
| Score of 0 to 1 on modified Rankin scale at 90 days — no./total no. (%) | 273/414 (65.9) | 229/417 (54.9) | 1.20 (1.07 to 1.34) |
| **Secondary clinical outcomes** | | | |
| Score on modified Rankin scale | | | |
| Median score at 90 days (IQR) | 1 (0 to 2) | 1 (0 to 3) | |
| Score of 0–2 at 90 days — no./total no. (%) | 333/414 (80.4) | 303/417 (72.7) | 1.11 (1.03 to 1.19) |
| Score of 0–3 at 90 days — no./total no. (%) | 365/414 (88.2) | 354/417 (84.9) | 1.04 (0.98 to 1.10) |
| NIHSS score† | | | |
| Median score at 24–72 hr (IQR) | 3 (1 to 6) | 4 (2 to 6) | 0.00 (–0.71 to 0.71) |
| Median score at 5–7 days or discharge (IQR) | 2 (1 to 4) | 2 (1 to 5) | –0.21 (–0.92 to 0.49) |
| Barthel Index of 95 or 100 at 90 days — no./total no. (%)‡ | 319/414 (77.1) | 294/417 (70.5) | 1.09 (1.01 to 1.19) |
| Median score on EQ-5D-5L at 90 days (IQR)§ | 1 (0.88 to 1) | 0.96 (0.84 to 1) | 0.03 (–0.01 to 0.07) |
| Radiologic intracranial hemorrhage — no./total no. (%) | 22/414 (5.3) | 14/418 (3.3) | 1.58 (0.82 to 3.06) |
| **Safety outcomes** | | | |
| Death — no./total no. (%) | 17/414 (4.1) | 16/417 (3.8) | 1.07 (0.55 to 2.09) |
| Intracranial hemorrhage — no./total no. (%)¶ | | | |
| Symptomatic within 36 hr | 7/414 (1.7) | 0 | 1.71 (0.45 to 2.97) |
| Asymptomatic | 15/414 (3.6) | 14/418 (3.3) | 1.07 (0.52 to 2.19) |



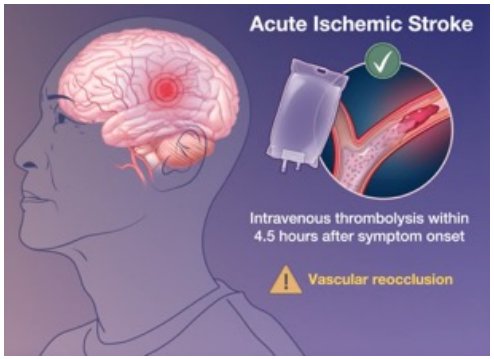

**Distribution of Functional Outcomes at 90 Days in the Modified Intention-to-Treat Population.**

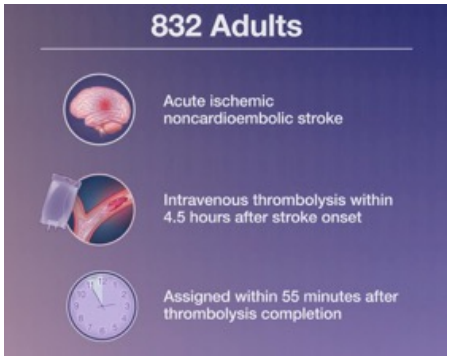
Shown are scores on the modified Rankin scale for the patients in the tirofiban group and the placebo group. One patient was lost to follow-up before 90 days. Scores range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight disability (patients are able to look after their own affairs without assistance but are unable to carry out all previous activities), 3 moderate disability (patients require some help but are able to walk unassisted), 4 moderately severe disability (patients are unable to attend to bodily needs without assistance and are unable to walk unassisted), 5 severe disability (patients require constant nursing care and attention), and 6 death. The primary efficacy and safety analyses were conducted according to the modified intention-to-treat principle and included all the patients who had provided consent, undergone randomization, and completed the 90-day follow-up.

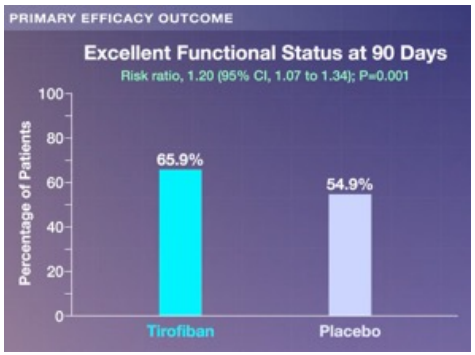


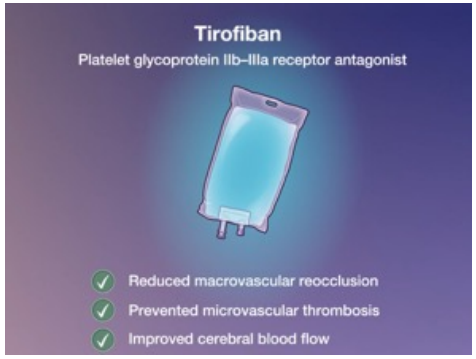

**Subgroup Analysis of the Primary Outcome.**

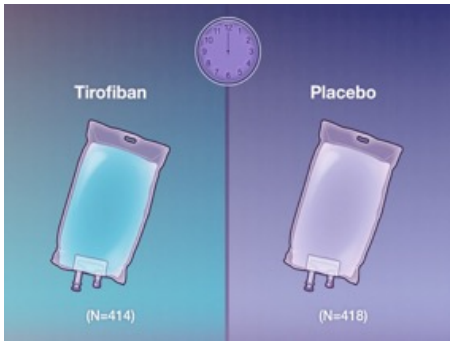
Shown is a forest plot comparing the tirofiban group with the placebo group according to subgroup with respect to the finding of a score of 0 or 1 on the modified Rankin scale at 90 days (the primary outcome). The trial was not powered and had no prespecified correction for multiple comparisons for a definitive analysis of subgroups. The risk ratios were adjusted for covariates with the use of the same multivariable-analysis approach used in the main analysis. Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating greater neurologic deficits. A score of 8 on this scale indicates a moderate or severe stroke. The Noncontrast Computed Tomography Alberta Stroke Program Early CT Score (NCCT ASPECTS) is a 10-point grading system, with lower scores indicating larger infarction. IVT denotes intravenous thrombolysis.

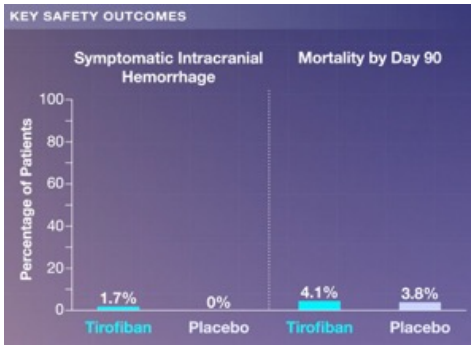

Acute Ischemic Stroke
Intravenous thrombolysis within 4.5 hours after symptom onset
Vascular reocclusion


832 Adults
Acute ischemic noncardioembolic stroke
Intravenous thrombolysis within 4.5 hours after stroke onset
Assigned within 55 minutes after thrombolysis completion

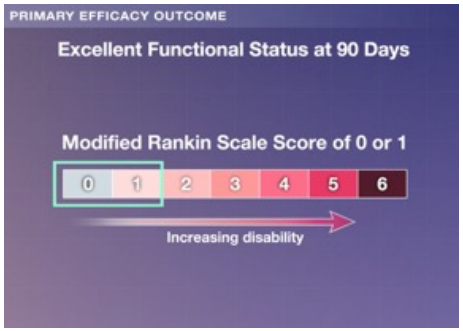

PRIMARY EFFICACY OUTCOME
Excellent Functional Status at 90 Days
Risk ratio, 1.20 (95% CI, 1.07 to 1.34); P=0.001
Percentage of Patients
100
80
60
40
20
0
65.9%
54.9%
Tirofiban
Placebo


Tirofiban
Platelet glycoprotein IIb–IIIa receptor antagonist
Reduced macrovascular reocclusion
Prevented microvascular thrombosis
Improved cerebral blood flow


Tirofiban
Placebo
(N=414)
(N=418)

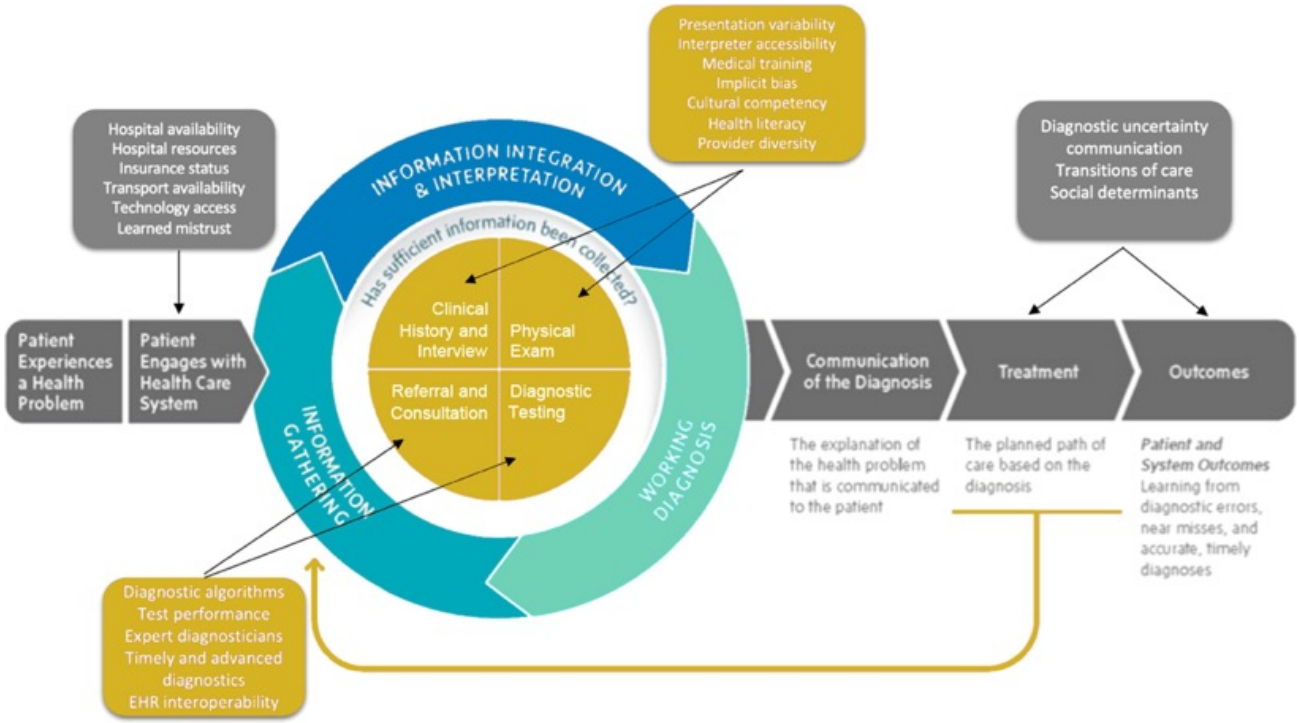

KEY SAFETY OUTCOMES
Symptomatic Intracranial Hemorrhage
Mortality by Day 90
Percentage of Patients
100
80
60
40
20
0
1.7%
0%
4.1%
3.8%
Tirofiban
Placebo
Tirofiban
Placebo


Improve outcomes
Early tirofiban infusion
After intravenous thrombolysis


PRIMARY EFFICACY OUTCOME
Excellent Functional Status at 90 Days
Modified Rankin Scale Score of 0 or 1
0
1
2
3
4
5
6
Increasing disability


Tirofiban
Increased the likelihood of excellent functional status at 90 days

Diagnostic equity is the principle that everyone should have an equal opportunity to receive an accurate and timely diagnosis, regardless of their race, gender, socioeconomic status, or other characteristics. It addresses disparities that can occur at any stage of the diagnostic journey, from a patient's initial awareness of a symptom to receiving a diagnosis and starting treatment. Achieving diagnostic equity involves understanding and eliminating systemic barriers within the healthcare system to ensure fair and just access to correct diagnostic pathways for all.



# Advancing Diagnostic Excellence through Medical Education in Diagnostic Equity

KEY POINTS

### Advancing Diagnostic Excellence through Medical Education in Diagnostic Equity

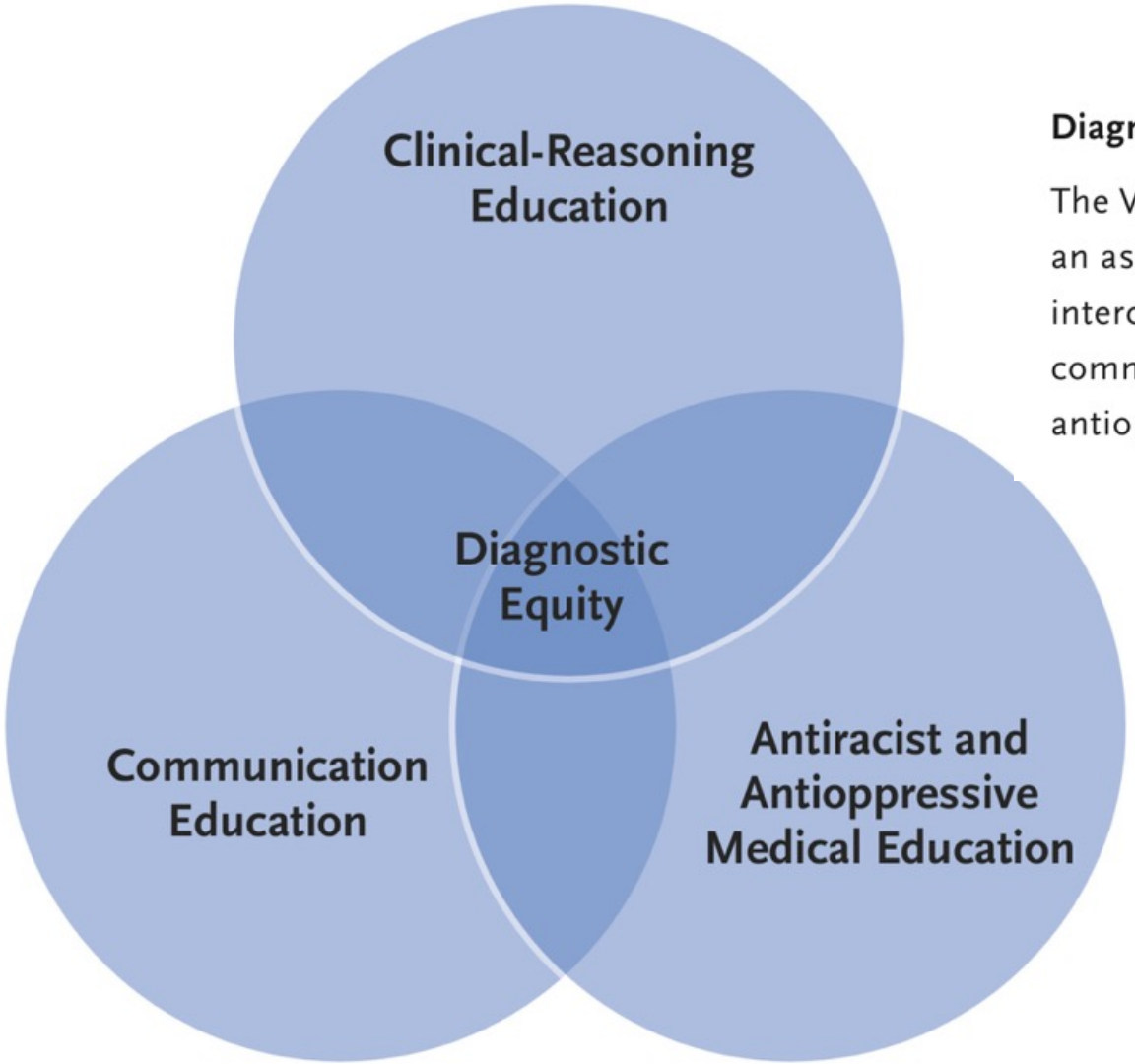
- Diagnostic inequities — the disproportionate burdens of diagnostic errors that are linked to patients' social identities (e.g., race, ethnic group, and gender) — are an important quality and safety problem standing in the way of diagnostic excellence.
- Medical education is one important lever that can support diagnostic equity by means of enhanced training; progress in medical education must be integrated with improvements in the closely linked clinical and research enterprises.
- A model to support education in diagnosis that integrates equity should include interventions on intrapersonal, interpersonal, systemic, and structural levels.
- Such a model should include teaching about diagnostic inequities; discussing diagnosis as a contextual, collaborative process; infusing clinicians' cognitive processes with equity considerations; creating opportunities to learn and practice equitable diagnostic communication; and modeling strategies to empower the full diagnostic team.
- Clinician–educators can draw on their expertise in and familiarity with communication and teamwork to model and teach about diagnostic equity.


**A Missed Diagnostic Opportunity.**

Clinicians can reduce the incidence of missed opportunities by pursuing IBRM training,[14] asking open-ended questions,[15,16] building rapport with patients using relationship-centered communication,[16] and getting to know each patient as a unique individual.[17] Example phrases adapted from the Relationship-Centered Communication approach of the Academy of Communication in Healthcare.[16] EMR denotes electronic medical record.

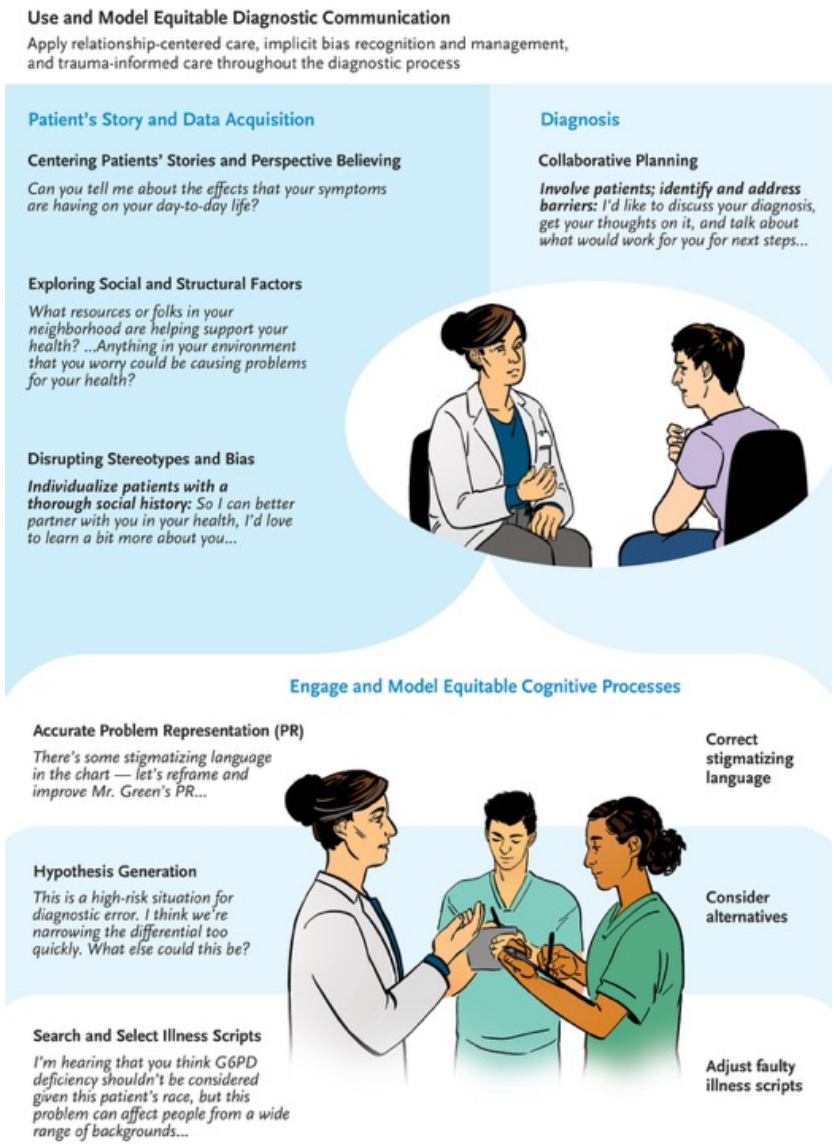
"Phuong" ist ein vietnamesischer Vorname.

Vielleicht ist Dr. Solas einfach schlecht ausgebildet.




**Diagnostic Equity.**

The Venn diagram shows diagnostic equity as an aspirational outcome resulting from the interconnection of clinical reasoning, communication, and antiracist and antioppressive education.




**Incorporating Equity Promoters into the Diagnostic-Reasoning Cognitive Framework.**

Adapted from Bowen.[55]

## Conclusion

Intentional integration of health equity into medical education involves building local expertise, managing resistance to change, and countering the inertia of large academic institutions. Without being intentional and rigorous in this pursuit, we risk perpetuating the status quo while simultaneously criticizing the lack of progress in years to come. We have an opportunity to contribute to a sustainable movement for change in medical education, which can support multipronged, interprofessional efforts aligning education, clinical practice, advocacy, and research with the aim of achieving health equity. Education focused on diagnostic equity is an important piece of this puzzle.

Embodying antioppressive approaches as educators requires actively working against entrenched systems and maintaining openness to continue learning from colleagues, students, trainees, and those seeking health care to facilitate personal and institutional growth. Although the specific focus on diagnostic equity is young, the health-equity field is not. We have drawn on and integrated lessons from the expansive literature on diagnostic reasoning, health equity, implicit bias, structural competency, and health care communication to develop a foundation for effective education in diagnostic equity. As healers and educators, we have an opportunity and responsibility to keep pushing forward to enhance equity and justice in health care in collaboration with the communities we serve. Diagnostic equity is a critical domain in need of focused attention and ripe for action by means of medical education.

**Diagnostic inequity** wird im Deutschen meist als **„diagnostische Ungleichheit“** oder im weiteren Sinne als Teil der **„sozial bedingten Ungleichheit von Gesundheitschancen“** bezeichnet. Gemeint ist, dass verschiedene Bevölkerungsgruppen – zum Beispiel aufgrund von sozialem Status, Herkunft, Geschlecht oder Einkommen – nicht die gleichen Chancen auf eine frühzeitige, präzise und angemessene medizinische Diagnose haben. Das führt dazu, dass Krankheiten bei bestimmten Gruppen häufiger zu spät oder gar nicht erkannt werden und ihre Behandlungschancen dadurch schlechter sind.

**Hintergrund und Kontext:**

•Diagnostische Ungleichheit ist ein Spezialfall der allgemeinen gesundheitlichen Ungleichheit (Health Inequities).
•Ursachen sind zum Beispiel Sprachbarrieren, Diskriminierung, mangelndes Wissen über Symptome oder schlechter Zugang zu medizinischer Versorgung.
•Besonders betroffen sind oft Menschen mit niedrigem sozioökonomischen Status, Migrationshintergrund oder geringer Bildung.

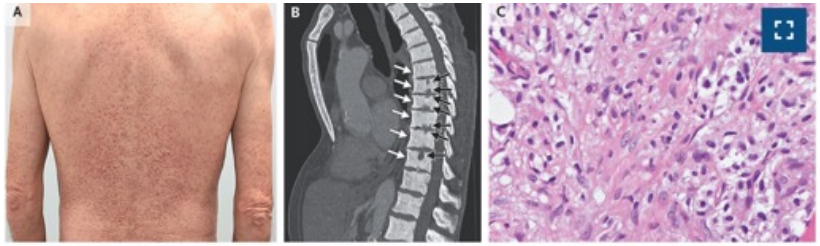
**Actionables – Das können Sie konkret tun:**

•Achten Sie auf Ihre eigenen Vorurteile in Gesprächen oder Untersuchungen.
•Fordern Sie bei Arztbesuchen aktiv verständliche Erklärungen und Zweitmeinungen ein.
•Nutzen Sie Beratungsstellen oder Patientenvertretungen.
•Unterstützen Sie Initiativen, die sich für gleiche Gesundheitschancen einsetzen.

**Alternative Sichtweisen & seltene Fälle:**

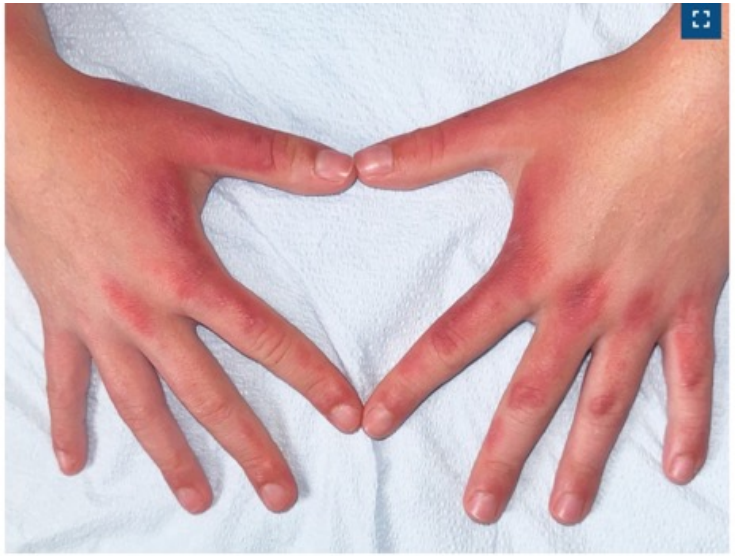
•Manche Fachleute betonen, dass nicht jede Ungleichheit automatisch ungerecht ist – individuelle Gesundheitsunterschiede können auch biologisch oder genetisch bedingt sein.
•Es gibt auch Kritik, dass der Begriff zu breit gefasst werden kann und dabei strukturelle Ursachen (wie Armut) und individuelle Faktoren (wie Gesundheitsverhalten) vermischt werden.

# Systemic Mastocytosis




A 65-year-old man presented to the internal medicine clinic with a 4-month history of a rash and a 2-month history of diarrhea and unintentional weight loss. Physical examination was notable for a maculopapular eruption on the trunk (Panel A), arms, and legs. Laboratory testing showed normocytic anemia and a serum tryptase level of more than 200 μg per liter (reference value, <11). Computed tomography of the abdomen and pelvis showed osteosclerosis of the thoracic vertebral bodies (Panel B, white arrows; sagittal view) and erosions of the end plates (Panel B, black arrows). No hepatosplenomegaly was seen. Skin biopsy revealed mast-cell infiltration. Bone marrow biopsy revealed cohesive groups of round and spindle-shaped cells with dense chromatin and eosinophilic cytoplasm and marked collagen fibrosis (Panel C, hematoxylin and eosin stain). Immunohistochemical staining was positive for CD25 and CD117 (c-Kit), which regulates mast-cell development and is mutated in a variety of cancers. Molecular testing identified the gain-of-function D816V mutation in *KIT*. A diagnosis of systemic mastocytosis — a condition characterized by mast-cell infiltration of organs, such as the bone marrow, liver, gastrointestinal tract, and cortical bone — was made. Treatment with antihistamines and the c-Kit inhibitor midostaurin was initiated. At 1 year of follow-up, the patient's symptoms had abated.

# Doxycycline-Induced Phototoxicity

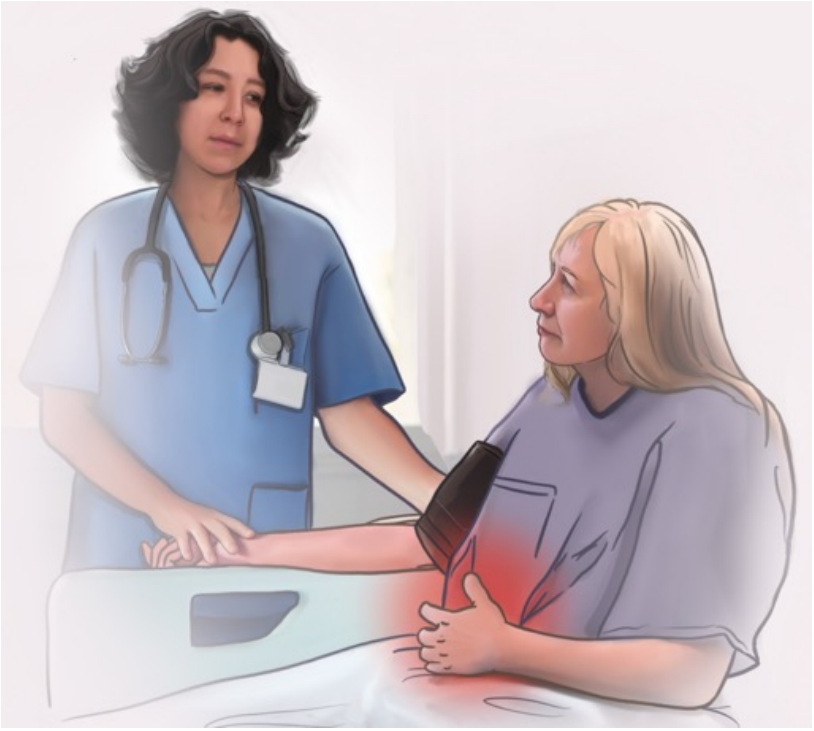


A 15-year-old girl with a history of acne vulgaris presented to the dermatology clinic with a 2-week history of a progressively worsening painful, blistering rash on both hands. One week before the onset of the rash, she had started taking oral doxycycline for treatment of her acne. She routinely played outdoors on park swings without sun protection. On physical examination, erythematous plaques with scattered vesicles were noted across the backs of her fingers, most prominently on the dorsal aspect of the thumbs and dorsolateral side of the index fingers. A diagnosis of doxycycline-induced phototoxicity was made. Doxycycline-induced phototoxicity is a dose-dependent reaction involving sun-exposed areas of the skin. Owing to the fact that the dorsal thumbs and dorsolateral index fingers are directly exposed to the sun regardless of specific outdoor activity, the development of a rash on those areas may be a helpful physical examination finding in identifying phototoxic drug reactions. Doxycycline was discontinued, and treatment with topical clobetasol was given. In the days after presentation, the rash resolved.

# A Fizzy Fix

## A Case from Brigham and Women's Hospital

The health care system needs to be fixed



She reported decreased appetite during this period as well as nonbilious, nonbloody vomiting. She described burning abdominal pain over the previous month, occurring in the upper abdomen and right side and wrapping around to her back. She did not think that this pain was related to food intake. Over-the-counter omeprazole and famotidine did not decrease the pain or nausea. She attributed her symptoms to increased stress.

She reported weight loss of 18 kg (19.4% of total body weight) over the past year, which had accelerated in the past month. She attributed her weight loss to having started treatment with semaglutide 1 year earlier, when her body-mass index (the weight in kilograms divided by the square of the height in meters) was approximately 32.

## Medical History

Anxiety

Stage 2 chronic kidney disease (baseline creatinine level, approximately 1.0 mg per deciliter; baseline glomerular filtration rate, approximately 65 ml per minute per 1.73 $m^2$ of body-surface area)

Chronic obstructive pulmonary disease

Lumbar radiculopathy with chronic back pain

Depression

Gastroesophageal reflux disease

Hyperlipidemia

Essential hypertension

Opioid use disorder

Type 2 diabetes mellitus

Iatrogenic condition

## Surgical History

Knee cartilage surgery 15 years before the current presentation

Throat surgery

## Social History

Reports interpersonal stress and is in the process of a move to a different house

Smoked a half pack of cigarettes daily for 40 years but stopped more than 10 years before the current presentation

Reports no use of alcohol or illicit drugs

Reports long-term clinic-supervised use of methadone for back pain

## Medications

16 meds never even metioned as a problem

Albuterol, 90 µg per actuation, one puff every 6 hours as needed

Alprazolam, 0.5-mg tablet once nightly

Amlodipine, 5 mg once daily

Aspirin, 81 mg once daily

Budesonide–formoterol, 160 µg and 5.6 µg per actuation, respectively, two puffs twice daily

Buspirone, 10 mg once daily

Gabapentin, 300 mg three times daily

Hydrochlorothiazide, 12.5 mg once daily

Lisinopril, 5 mg once daily

Metformin, 500 mg once daily

Methadone, 30 mg once daily

Omeprazole, 20 mg once daily

Roflumilast, 500 µg once daily

Rosuvastatin, 40 mg once daily

Semaglutide, 2 mg once weekly

Tramadol, 50 mg every 6 hours as needed for pain

Drugs that delay gastric emptying

# Physical Examination

## Vital signs

Temperature, 36.8°C (oral)

Heart rate, 60 beats per minute

Blood pressure, 109/47 mm Hg

Respiratory rate, 18 breaths per minute

Oxygen saturation, 96% while breathing ambient air

Height, 170.2 cm

Weight, 75 kg

Body-mass index, 25.9

## General appearance

Uncomfortable-appearing but in no acute distress

## Head, eyes, ears, nose, and throat

Mucous membranes moist

## Heart

Regular rate and rhythm

No murmurs, rubs, or gallops

## Skin

No erythema, rash, or cyanosis

## Lungs

Clear on auscultation

No increased work of breathing or use of accessory muscles

No wheezes, rales, or rhonchi

## Abdomen

Bowel sounds present

Negative Murphy's sign

Abdomen soft and nondistended

On admission tender to palpation over right abdomen

## Arms and Legs

Warm and well-perfused

No edema

Capillary refill of less than 2 seconds

## Lymph nodes

No palpable cervical lymphadenopathy

## Nervous system

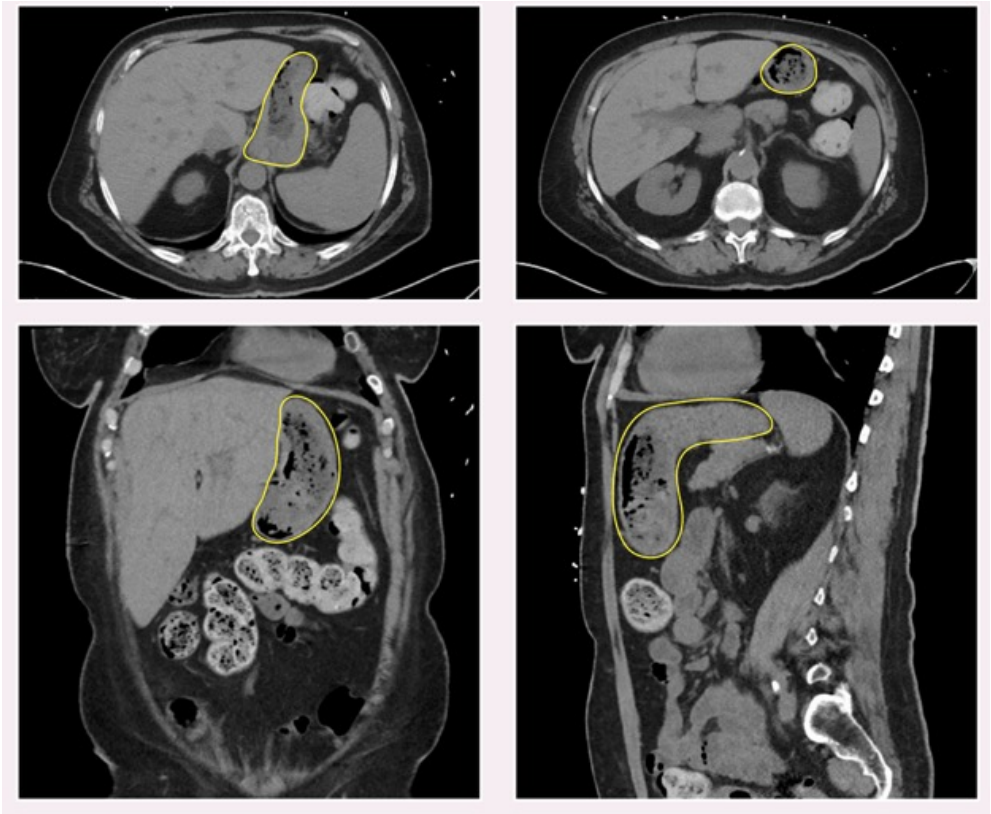
Awake and alert

Responds to questions appropriately

Oriented to time, person, place, and situation

# Hypokaliämie, CKD Stadium IV (wahrscheinlich CKD+AKI) und mikrozytäre Anemie

| Variable | Result | Normal Range | Flag |
|---|---|---|---|
| Sodium (mmol/liter) | 136 | 136–142 | – |
| Potassium (mmol/liter) | 3.2 | 3.5–5.0 | Low |
| Chloride (mmol/liter) | 97 | 98–108 | Low |
| Bicarbonate (mmol/liter) | 25 | 25–32 | – |
| Urea nitrogen (mg/dl) | 39 | 9–25 | High |
| Creatinine (mg/dl) | 3.07 | 0.70–1.30 | High |
| Estimated glomerular filtration rate (ml/min/1.73 $m^2$) | 16 | >60 | Low |
| Glucose (mg/dl) | 109 | <100 (fasting) | – |
| Alanine aminotransferase (U/liter) | 13 | 10–50 | – |
| Aspartate aminotransferase (U/liter) | 24 | 10–50 | – |
| Alkaline phosphatase (U/liter) | 46 | 40–130 | – |
| Total protein (g/dl) | 6.8 | 6.4–8.3 | – |
| Albumin (g/dl) | 4.1 | 3.5–5.2 | – |
| Total bilirubin (mg/dl) | 0.3 | 0.0–1.0 | – |
| Direct bilirubin (mg/dl) | <0.2 | 0.0–0.3 | – |
| White-cell count (per $mm^3$) | 7670 | 4000–10,000 | – |
| Hematocrit (%) | 29.4 | 36.0–48.0 | Low |
| Hemoglobin (g/dl) | 9.8 | 11.5–16.4 | Low |
| Reticulocyte count (%) | 0.9 | 0.6–2.8 | – |
| Mean corpuscular volume (fl) | 84.5 | 80.0–100.0 | – |
| Red-cell distribution width (%) | 12.9 | 12.1–16.0 | – |
| Nucleated red cells (per 100 white cells) | 0 | 0 | – |
| Platelet count (per $mm^3$) | 230,000 | 150,000–450,000 | – |
| Iron (ug/dl) | 71 | 37–145 | – |
| Ferritin (ug/liter) | 79 | 13–150 | – |
| Iron saturation (%) | 26 | 20–40 | – |
| Total iron binding capacity (ug/dl) | 272 | 250–450 | – |
| Vitamin $B_{12}$ (pg/ml) | 535 | 211–946 | – |
| Folate (ng/ml) | 7.9 | 3.1–17.5 | – |



The cost of Magnetic Resonance Cholangiopancreatography (MRCP) in the US varies significantly, but the average out-of-pocket cost can be around $4,656

**Imaging Studies**

**Computed Tomography (CT)**

CT of the abdomen and pelvis, performed without contrast enhancement owing to acute kidney injury, showed moderate bile-duct dilatation to the level of the ampulla, without discernible radiodense stones. The stomach was moderately distended with semisolid material. No focal liver lesions were observed. Heavy stool burden was appreciated without evidence of bowel obstruction.

**MRI**

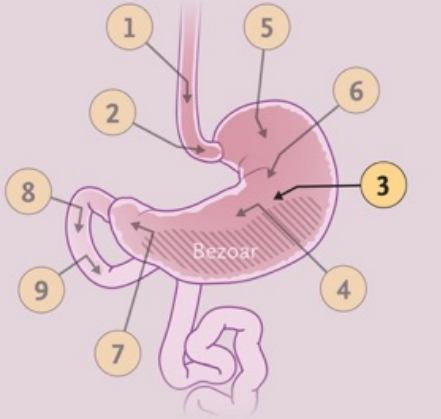
Magnetic resonance cholangiopancreatography showed extrahepatic ductal dilatation, with the common bile duct measuring up to 1.4 cm in diameter. No choledocholithiasis or obstructing mass was identified. These findings were considered to be most likely related to nonobstructive biliary dilation in the context of chronic opioid use.

Imaging also revealed a mass in the stomach with mottled features that were considered to be most likely caused by trapped air.

# Clinical Course and Initial Management

The patient had persistent nausea and vomiting on the day of hospital admission. She provided additional history, reporting that a few months earlier she had taken approximately 24 tablets of ibuprofen in 1 week for her chronic back pain. Following magnetic resonance cholangiopancreatography, the differential diagnosis for the observed nonobstructive biliary dilatation included chronic opioid use, gastric bezoar, or potentially both. Use of semaglutide or opioids may cause delayed gastric emptying, which increases risk for bezoar formation. In addition, CT imaging aroused concern for accumulation of semisolid material in the stomach. Peptic ulcer disease was also considered, given her symptoms and use of ibuprofen. Esophagogastroduodenoscopy (EGD) was performed.

**Initial EGD**

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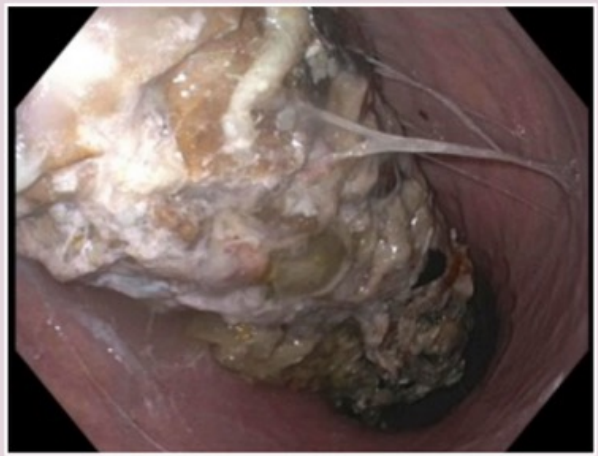


**3. Gastric Body**

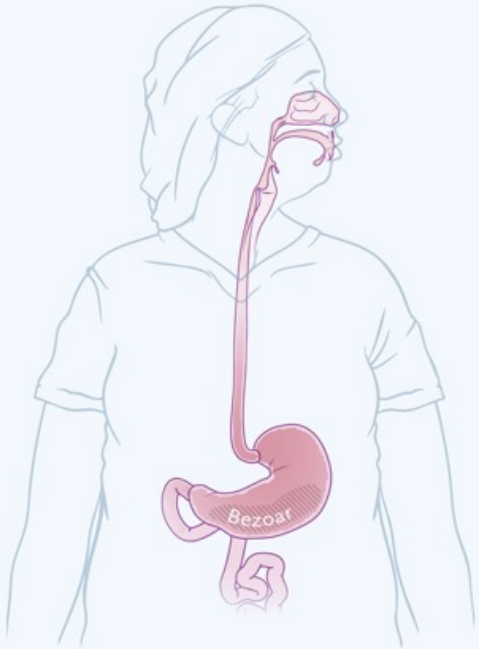
# The Basics of Gastric Bezoars

LEARNING MODULE

## Presentation

Gastric bezoars may be found incidentally in an asymptomatic patient.

When symptomatic, patients may present with nonspecific gastrointestinal symptoms including pain, nausea, vomiting, and abdominal discomfort. Patients may also present with signs of bleeding due to ulceration, including bloody or tarry stool, hematemesis, and anemia.




## Etiologies

Bezoars are classified on the basis of their composite materials.

- **Phytobezoars** are formed from fruit or vegetable material.
- **Trichobezoars** are formed from ingested hair and are associated with trichotillomania and coincident psychiatric conditions.
- **Pharmacobezoars** are formed from medications and are associated with excessive pill consumption as seen in cases of attempted suicide. They may cause an extended period of drug absorption.

Other types are also described, including lactobezoars (composed of milk protein) in infants, and foreign-body bezoars.

## Epidemiologic Features

Gastric bezoars are uncommon in the general population. The risk is higher in persons who ingest certain foods (e.g., persimmons, pineapples, raisins, and celery).

Available data suggest that gastric bezoars are detected in fewer than 0.5% of esophagogastroduodenoscopies. Reduced gastric motility may contribute to bezoar development. There are several possible contributing factors:

- **Anatomical causes** such as postsurgical changes (including changes related to bariatric or other gastric surgery).
- **Medical conditions** such as delayed gastric emptying, diabetes, and autonomic neuropathy.
- **Medications** affecting gastric motility, including glucagon-like peptide-1 receptor agonists, narcotic agents (both of which this patient was taking), and tricyclic antidepressants.

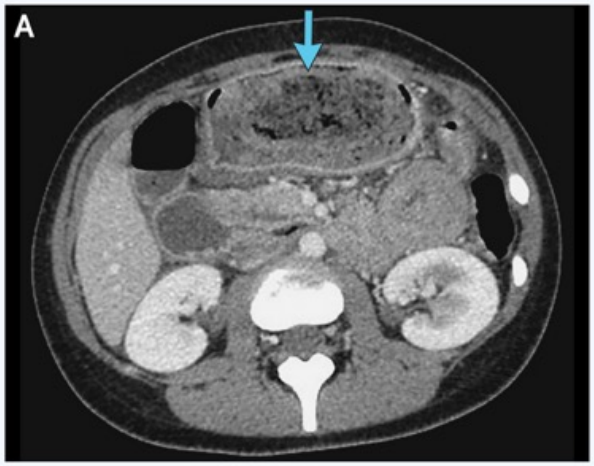
# Dies ist nicht unsere Patientin

## Diagnosis

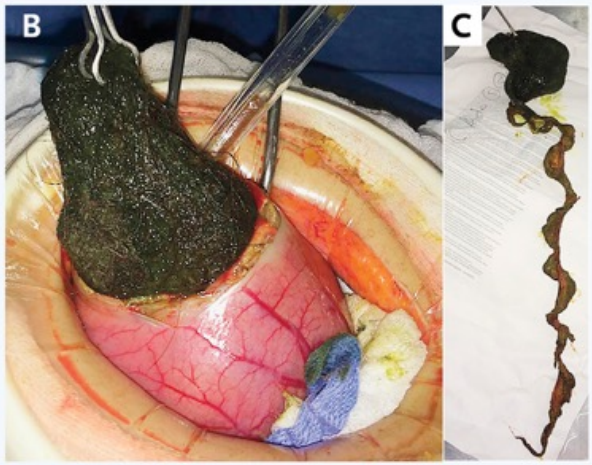
Diagnosis may be made on the basis of imaging or upper endoscopy.

Computed tomography may show a gastric mass. The diagnosis is supported by the presence of a mass with a mottled appearance that is caused by air trapped within the bezoar.

The diagnosis is typically evident on endoscopy, where a collection of consumed material is found.




Panel A shows CT revealing a trichobezoar (arrow).




Panel B shows surgical removal of a trichobezoar, and Panel C a trichobezoar after removal.

# What Would You Do?

## In addition to the discontinuation of semaglutide, which of the following choices would be most appropriate for initial management of a gastric bezoar and persistent nausea and vomiting?

Select a strategy to see whether it is an appropriate choice and to learn about the probable outcome. You will be able to return to the list of choices to review the probable consequences of each choice.

Percentages associated with each management option represent reader responses.

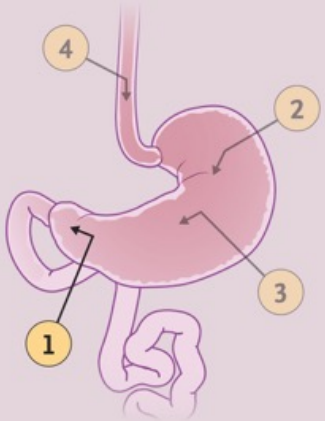
# Chemical Dissolution

Semaglutide was discontinued on admission to the hospital.

Chemical dissolution with cola was attempted. Diet cola was recommended owing to the patient's history of diabetes. The plan to administer 3000 ml of cola over a 12-hour period was modified to administration of approximately 1500 ml per day because of the patient's reluctance to consume carbonated beverages, which she did not enjoy.

On the second day of administration of the diet cola, the patient reported a sudden tugging sensation in her abdomen, followed by a prompt decrease in her nausea and abdominal discomfort. A repeat EGD showed that the bezoar was no longer present.

**EGD after Bezoar Removal**

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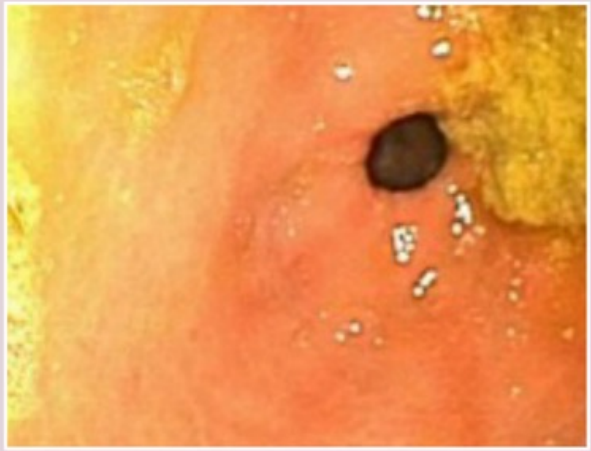


**1. Prepyloric Stomach**

How much did this hospitalization at the Peter Bent Brigham Hospital cost?

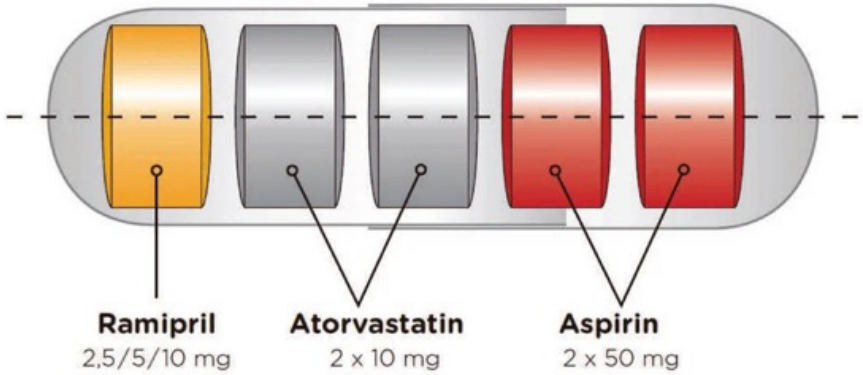

Problem gelöst !!!

## Patient Outcome

In the hospital, the patient transitioned to a regular diet with no adverse effects, and at the time of discharge, she had no nausea, vomiting, or abdominal pain. Semaglutide was not resumed; methadone and tramadol, as needed, were continued. The patient began treatment with twice-daily omeprazole. After discharge, she had an increase in appetite, and her weight increased from 74 kg at discharge to 84 kg 3 months later (BMI increased to 29). Her hemoglobin A1c was 6.6% 3 months after hospitalization (increased from 6.3% 2 months before hospitalization). She was advised to follow up with her primary care provider for a gastric-emptying study. Although this study has not yet been completed, she reported complete symptom resolution at subsequent primary care visits over the next several months.

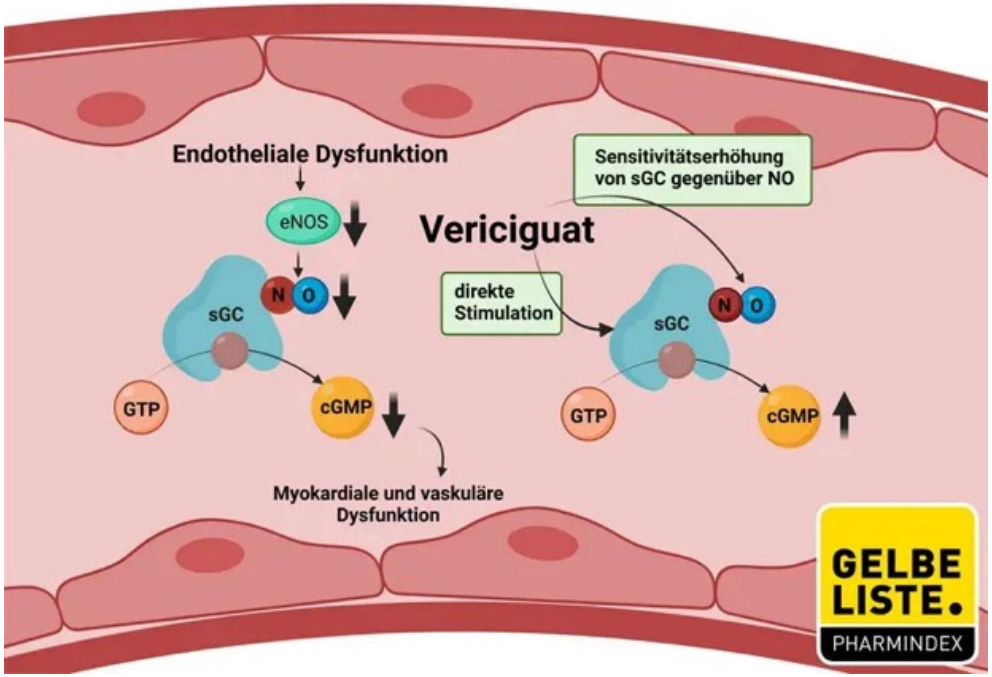
Cola dissolves bezoars through a combination of factors including its acidic nature, the mucolytic (mucus-dissolving) effect of sodium bicarbonate, and the physical action of carbon dioxide ($CO_2$) bubbles that penetrate and break down the fibrous material of the bezoar. The carbonic and phosphoric acids in cola provide a low pH, similar to stomach acid, which helps to break down the fibrous components of the bezoar. The $CO_2$ bubbles, generated from the sodium bicarbonate, help to increase the surface area of the bezoar and facilitate its disintegration.

Eine Polypille ist eine Tablette, die mehrere Wirkstoffe in niedriger Dosierung kombiniert, um das Risiko für Herz-Kreislauf-Erkrankungen zu reduzieren und die Medikamenteneinnahme zu vereinfachen. Sie enthält in der Regel Medikamente zur Blutdrucksenkung, zur Cholesterinsenkung (Statine) und Blutverdünner. Die Polypille verbessert die Adhärenz (Medikamententreue) und kann die Behandlung für Hochrisikopatienten bezahlbar machen und deren klinische Ergebnisse verbessern.




THE LANCET

Verquvo® (Vericiguat) ist zugelassen zur Behandlung von symptomatischer, chronischer Herzinsuffizienz bei erwachsenen Patienten mit reduzierter Ejektionsfraktion, die nach einem kürzlich aufgetretenen Dekompensationsereignis, das eine i.v.-Therapie erforderte, stabilisiert wurden. Vericiguat stimuliert die lösbare guanylatzyklase und dadurch wird cGMP produziert.



# Vericiguat in patients with chronic heart failure and reduced ejection fraction (VICTOR): a double-blind, placebo-controlled, randomised, phase 3 trial


## Summary

**Background** Vericiguat is indicated to reduce the risk of cardiovascular death and hospitalisation for heart failure in patients with heart failure and reduced ejection fraction (HFrEF) following a recent worsening event. The aim of the VICTOR trial was to assess the effect of vericiguat in patients with HFrEF without recent heart failure worsening.

**Methods** In this double-blind, placebo-controlled, phase 3 trial, conducted at 482 sites across 36 countries, patients aged 18 years or older with HFrEF (left ventricular ejection fraction of ≤40%) without heart failure hospitalisation within 6 months or outpatient intravenous diuretic use within 3 months before randomisation were randomly assigned (1:1) using an intervention randomisation system with interactive response technology to oral vericiguat (target 10 mg dose) or matching placebo. The primary composite endpoint was time to cardiovascular death or heart failure hospitalisation. Efficacy endpoints were assessed in the intention-to-treat population. Adverse events were assessed in all randomly assigned patients who received at least one dose of study drug (safety population). This trial is registered with ClinicalTrials.gov, NCT05093933, and is complete.

**Findings** Between Nov 2, 2021, and Dec 21, 2023, 10 921 patients were screened and 6105 were randomly assigned: 3053 to vericiguat and 3052 to placebo. The median age was 68·0 years (IQR 61·0–75·0), 1440 (23·6%) patients were women, 4665 (76·4%) were men, 3934 (64·4%) were White, and 2899 (47·5%) had no previous hospitalisation for heart failure. During a median follow-up of 18·5 months (IQR 13·6–24·7), primary outcome events occurred in 549 (18·0%) patients in the vericiguat group and 584 (19·1%) patients in the placebo group (hazard ratio [HR] 0·93 [95% CI 0·83–1·04]; p=0·22). As prespecified in the protocol, because the primary endpoint was not statistically significant, all analyses of secondary and exploratory endpoints are considered nominal. Cardiovascular death occurred in 292 (9·6%) patients in the vericiguat group and 346 (11·3%) patients in the placebo group (HR 0·83 [95% CI 0·71–0·97]). Hospitalisation for heart failure occurred in 348 (11·4%) patients in the vericiguat group and in 362 (11·9%) patients in the placebo group (HR 0·95 [95% CI 0·82–1·10]). Serious adverse events occurred in 717 (23·5%) of 3049 patients in the vericiguat group and 751 (24·6%) of 3049 patients in the placebo group. The most common adverse event was symptomatic hypotension (345 [11·3%] patients in the vericiguat group and 281 [9·2%] in the placebo group). All-cause death occurred in 377 (12·3%) patients in the vericiguat group and 440 (14·4%) patients in the placebo group (HR 0·84 [95% CI 0·74–0·97]).

**Interpretation** Among patients with HFrEF and no recent worsening, vericiguat did not reduce the risk of a composite endpoint of time to cardiovascular death or heart failure hospitalisation. Fewer cardiovascular deaths were observed in the vericiguat group than in the placebo group.



**Funding** Merck Sharp & Dohme (a subsidiary of Merck) and Bayer.

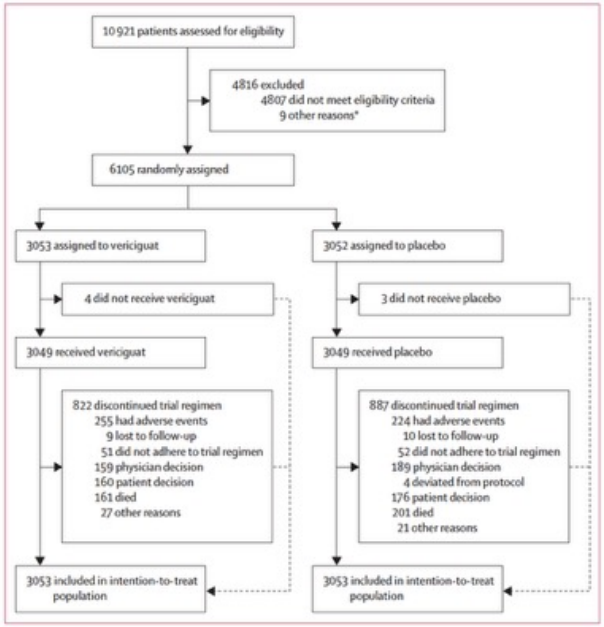



*Figure 1:* Trial profile

| | Vericiguat group (n=3053) | Placebo group (n=3052) |
|---|---|---|
| Age, years | 68·0 (61·0–75·0) | 68·0 (61·0–75·0) |
| Sex | | |
| Male | 2326 (76·2%) | 2339 (76·6%) |
| Female | 727 (23·8%) | 713 (23·4%) |
| Race | | |
| White | 1942 (63·6%) | 1992 (65·3%) |
| Asian | 383 (12·5%) | 363 (11·9%) |
| Black* | 343 (11·2%) | 313 (10·3%) |
| Multiracial | 313 (10·3%) | 330 (10·8%) |
| American Indian or Alaskan | 159 (5·2%) | 142 (4·7%) |
| Native Hawaiian or Pacific Islander | 4 (0·1%) | 7 (0·2%) |
| Not reported | 1 (<0·1%) | 0 |
| Geographical region | | |
| Latin and South America | 888 (29·1%) | 887 (29·1%) |
| Eastern Europe | 823 (27·0%) | 877 (28·7%) |
| Western Europe | 586 (19·2%) | 541 (17·7%) |
| Asia–Pacific | 432 (14·2%) | 422 (13·8%) |
| North America | 324 (10·6%) | 325 (10·6%) |
| Comorbidities | | |
| Diabetes | 1274 (41·7%) | 1311 (43·0%) |
| Use of GLP-1 receptor agonists | 113/1274 (8·9%) | 118/1311 (9·0%) |
| Atrial fibrillation | 1135 (37·2%) | 1182 (38·7%) |
| Hypertension | 2153 (70·5%) | 2176 (71·3%) |
| Coronary artery disease | 1861 (61·0%) | 1883 (61·7%) |
| Systolic blood pressure, mm Hg | 120·6 (15·8) | 121·5 (16·3) |
| Haemoglobin, g/dL | 14·2 (3·1) | 14·2 (1·8) |
| BMI, kg/m² | 27·5 (24·3–31·3) | 27·7 (24·7–31·4) |
| NT-proBNP, pg/mL | 1370 (826–2338) | 1381 (828–2430) |
| Hospitalisation for heart failure | | |
| 6–12 months before randomisation | 424 (13·9%) | 435 (14·3%) |
| >12 months before randomisation | 1188 (38·9%) | 1129 (37·0%) |
| No previous hospitalisation for heart failure | 1426 (46·7%) | 1473 (48·3%) |

(Table 1 continues in next column)

(Continued from previous column)

| | Vericiguat group (n=3053) | Placebo group (n=3052) |
|---|---|---|
| NYHA class | | |
| II | 2411 (79·0%) | 2411 (79·0%) |
| III | 635 (20·8%) | 633 (20·7%) |
| IV | 7 (0·2%) | 8 (0·3%) |
| LVEF, % | 30·5% (7·0) | 30·4% (7·0) |
| eGFR, mL/min per 1·73 m² | 70·9 (23·8) | 70·8 (24·3) |
| <15 | 3 (0·1%) | 4 (0·1%) |
| ≥15 to <30 | 118 (3·9%) | 125 (4·1%) |
| ≥30 to <60 | 921 (30·2%) | 940 (30·8%) |
| ≥60 | 1954 (64·0%) | 1921 (62·9%) |
| Missing | 57 (1·9%) | 62 (2·0%) |
| Medical therapy | | |
| Loop diuretics | 2131 (69·8%) | 2129 (69·8%) |
| β blockers | 2886 (94·5%) | 2880 (94·4%) |
| Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker | 1150 (37·7%) | 1188 (38·9%) |
| Angiotensin receptor–neprilysin inhibitor | 1734 (56·8%) | 1682 (55·1%) |
| Mineralocorticoid receptor antagonist | 2358 (77·2%) | 2390 (78·3%) |
| SGLT2 inhibitor | 1812 (59·4%) | 1798 (58·9%) |
| Implantable cardioverter defibrillator | 993 (32·5%) | 1016 (33·3%) |
| Cardiac resynchronisation therapy | 464 (15·2%) | 440 (14·4%) |

Data are median (IQR), n (%), mean (SD), or n/N (%). Percentages might not sum to 100 because of rounding. eGFR=estimated glomerular filtration rate. LVEF=left ventricular ejection fraction. NT-proBNP=N-terminal pro-B-type natriuretic peptide. NYHA=New York Heart Association. *Includes participants who identify as Black or multiracial including Black.

***Table 1:*** **Baseline characteristics**

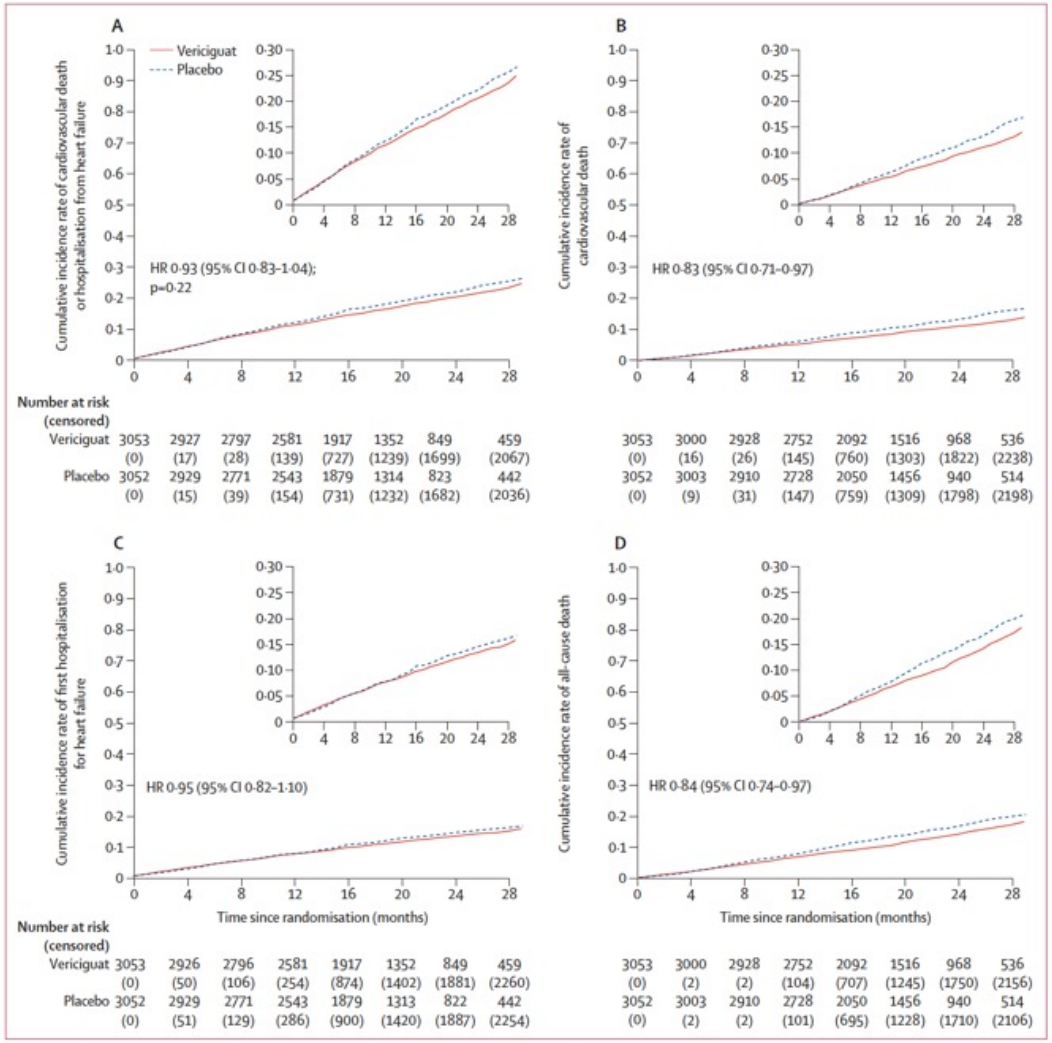



*Figure 2:* **Kaplan–Meier estimates of the cumulative incidence of the primary and secondary outcomes**
Death from cardiovascular causes or first hospitalisation for heart failure (A), cardiovascular death (B), first hospitalisation for heart failure (C), and all-cause death (D). The inset in each panel shows the same data on an enlarged y axis. HR=hazard ratio.

| | Vericiguat group (n=3053) | | Placebo group (n=3052) | | HR (95% CI) | p value |
|---|---|---|---|---|---|---|
| | Events (%) | Events per 100 patient-years | Events (%) | Events per 100 patient-years | | |
| **Primary composite outcome* and components** | | | | | | |
| Time from randomisation to cardiovascular death or hospitalisation for heart failure | 549 (18·0%) | 11·3 | 584 (19·1%) | 12·2 | 0·93 (0·83–1·04) | 0·22 |
| Cardiovascular death | 201 (6·6%) | .. | 222 (7·3%) | .. | .. | .. |
| Hospitalisation for heart failure | 348 (11·4%) | .. | 362 (11·9%) | .. | .. | .. |
| **Secondary outcomes** | | | | | | |
| Time from randomisation to cardiovascular death | 292 (9·6%) | 5·7 | 346 (11·3%) | 6·8 | 0·83 (0·71–0·97) | .. |
| Time from randomisation to first hospitalisation for heart failure | 348 (11·4%) | 7·2 | 362 (11·9%) | 7·6 | 0·95 (0·82–1·10) | .. |
| Total heart failure hospitalisation events (first and recurrent events) | 549 | 10·7 | 597 | 11·8 | 0·90 (0·80–1·02) | .. |
| Time from randomisation to all-cause death | 377 (12·3%) | 7·3 | 440 (14·4%) | 8·6 | 0·84 (0·74–0·97) | .. |
| **Exploratory outcomes** | | | | | | |
| Time from randomisation to first urgent heart failure visit or heart failure hospitalisation | 374 (12·3%) | 7·8 | 399 (13·1%) | 8·4 | 0·93 (0·80–1·07) | .. |
| Time from randomisation to first cardiovascular hospitalisation | 594 (19·5%) | 12·9 | 634 (20·8%) | 14·0 | 0·92 (0·83–1·03) | .. |

As prespecified in the protocol, formal hypothesis testing of secondary endpoints was not performed because the primary endpoint was not statistically significant; all secondary and exploratory endpoint analyses are nominal and provided for reference only. HR=hazard ratio. *If both first events contributing to the composite endpoint occurred on the same day, the composite event was attributed to cardiovascular death.

*Table 2:* **Primary, secondary, and exploratory outcomes**

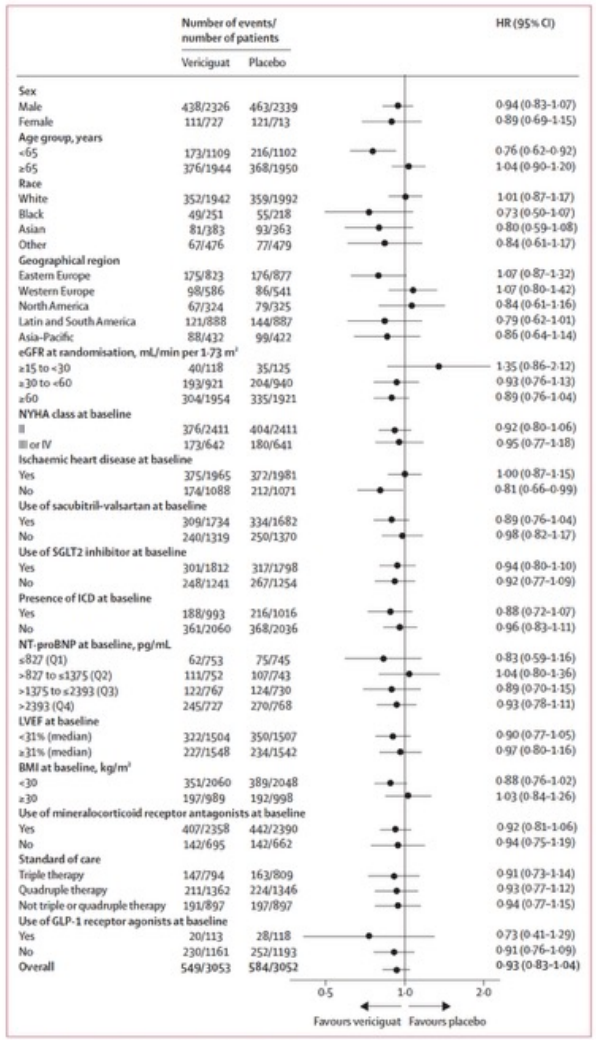



**Figure 3: Primary outcome in prespecified subgroups**
eGFR=estimated glomerular filtration rate. HR=hazard ratio. ICD=implantable cardioverter defibrillator. LVEF=left ventricular ejection fraction. NT-proBNP=N-terminal pro-B type natriuretic peptide. NYHA=New York Heart Association.

Although a numerical reduction in cardiovascular deaths was observed, vericiguat did not reduce the risk of hospitalisation for heart failure in this trial. A plausible explanation might be the unprecedented high use of guideline-directed medical therapy, including contemporary drug classes such as ARNIs and SGLT2 inhibitors in a population with overall low risk by design. Nearly four in five patients had NYHA class II symptoms, 47·5% had never previously been hospitalised for heart failure, and only 14% had been hospitalised within 1 year. By contrast, larger proportions of recently hospitalised patients have been reported in recent trials: 42% in PARADIGM-HF and 27% in DAPA-HF.[6,7] The high use of contemporary therapy and the lower proportion of recent hospitalisations might explain the delayed separation of the hospitalisation curves and lower risk reduction in heart failure hospitalisation seen in VICTOR. The reason for the observed mortality benefit in the absence of a reduction in heart failure hospitalisation is unclear and warrants further investigation.

The safety profile of vericiguat in VICTOR was similar to that observed in VICTORIA.[2] As anticipated, symptomatic hypotension and anaemia were more common in the patients receiving vericiguat than in those receiving placebo, but the overall frequency of adverse events was similar in the two groups.

Interpretation of the findings is limited by the neutral result for the primary endpoint, and therefore the secondary endpoint findings should be interpreted with caution. Exclusion of patients with NT-proBNP concentrations greater than 6000 pg/mL at screening might limit the generalisability of the VICTOR findings to patients with more advanced disease. In addition, subgroup analyses are exploratory in nature and were not powered to detect interaction effects.

In conclusion, although vericiguat did not reduce the risk of the composite endpoint of cardiovascular death or hospitalisation for heart failure in ambulatory patients with HFrEF on a background of high use of contemporary guideline-recommended medical therapy, fewer cardiovascular and all-cause deaths were observed with vericiguat than with placebo.

## Research in context

### Evidence before this study

Heart failure with reduced ejection fraction (HFrEF) is associated with a high risk of morbidity and mortality. Oral soluble guanylate cyclase stimulators enhance the nitric oxide–soluble guanylate cyclase–cGMP signalling pathway, which is commonly impaired in HFrEF, offering a mechanistically distinct approach that can improve myocardial and vascular function and reduce heart failure events in these patients. We searched PubMed for articles published from database inception to July 14, 2025, using the terms "vericiguat", "soluble guanylate cyclase stimulator", and "heart failure with reduced ejection fraction". Only the VICTORIA trial was identified as relevant. Reference lists of relevant articles and major heart failure guidelines were also reviewed. Our literature search showed that only one oral soluble guanylate cyclase stimulator, vericiguat, has been approved for the treatment of worsening HFrEF, on the basis of the results from the Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction (VICTORIA) trial, which showed a reduction in the risk of cardiovascular death or hospitalisation for heart failure in patients with HFrEF who had been hospitalised for heart failure within the previous 6 months or required outpatient intravenous diuretic therapy within the previous 3 months. However, the effect of vericiguat in ambulatory patients with HFrEF receiving contemporary medical therapy has not previously been assessed.

### Added value of this study

The Vericiguat in Adults with Chronic Heart Failure and Reduced Ejection Fraction (VICTOR) trial was designed to assess the effect of vericiguat on the risk of a primary composite endpoint of cardiovascular death or hospitalisation for heart failure in patients with HFrEF without recent worsening, thereby extending the findings of the VICTORIA trial to a broader, more stable ambulatory population. In this study, vericiguat did not reduce the risk of the primary endpoint compared with placebo. Fewer cardiovascular death and all-cause death events (secondary endpoints) were observed in the vericiguat group than in the placebo group.

### Implications of all the available evidence

Although vericiguat did not reduce the composite primary endpoint of cardiovascular death or hospitalisation for heart failure in ambulatory patients with HFrEF receiving contemporary guideline-directed medical therapy, the observed reduction in cardiovascular mortality suggests that vericiguat might provide a mortality benefit in this population.

# Vericiguat for patients with heart failure and reduced ejection fraction across the risk spectrum: an individual participant data analysis of the VICTORIA and VICTOR trials


## Summary

**Background** Following completion of the VICTORIA trial, vericiguat was approved for the treatment of worsening heart failure with reduced ejection fraction (HFrEF) and received a class IIb recommendation in European and North American guidelines. The subsequent VICTOR trial evaluated the use of vericiguat in patients with HFrEF and no recent worsening. We aimed to assess the effect of vericiguat on clinical endpoints through pooled analyses of patient-level data from the VICTORIA and VICTOR trials.

**Methods** This prespecified, pooled individual participant-level analysis was conducted on data from two trials: VICTORIA, which was active from Sept 25, 2016, to Sept 2, 2019 in 42 countries, and VICTOR, which was active from Nov 2, 2021, to Feb 5, 2025 in 36 countries. The VICTORIA trial enrolled adult (aged ≥18 years) participants with HFrEF with recent worsening (defined as either hospitalisation for heart failure within the previous 6 months or outpatient use of intravenous diuretics within the previous 3 months) and increased NT-proBNP concentrations; the VICTOR trial had similar eligibility criteria but participants had no recent worsening of heart failure. Participants in both trials received contemporary background guideline-directed heart failure therapy as appropriate. The primary endpoint was a composite endpoint of cardiovascular death or hospitalisation for heart failure (also assessed individually). This study is registered with PROSPERO, CRD420251065636.

**Findings** Data from 11 155 patients (5050 in the VICTORIA trial and 6105 in the VICTOR trial) were included in the pooled analysis. The primary endpoint of cardiovascular death or hospitalisation for heart failure occurred in 1446 (25·9%) of 5579 patients in the vericiguat group and 1556 (27·9%) of 5576 patients in the placebo group (hazard ratio [HR] 0·91 [95% CI 0·85–0·98]; p=0·0088), with similar reductions in its individual components of cardiovascular death (0·89 [0·80–0·98]; p=0·020) and hospitalisation for heart failure (0·92 [0·84–1·00]; p=0·043) as first events.

**Interpretation** Vericiguat reduced the risk of hospitalisation for heart failure and cardiovascular death in patients with HFrEF across a broad range of clinical severity, including those receiving contemporary guideline-directed medical therapy. Vericiguat might be suitable as an additional treatment option for selected patients with HFrEF.



**Funding** Merck Sharp & Dohme (a subsidiary of Merck) and Bayer.

| | Pooled trials (VICTOR and VICTORIA) | | | VICTOR (n=6105) | VICTORIA (n=5050) |
|---|---|---|---|---|---|
| | Vericiguat (n=5579) | Placebo (n=5576) | Pooled (n=11155) | | |
| Age (years) | 68·0 (60·0–76·0) | 68·0 (60·0–75·0) | 68·0 (60·0–75·0) | 68·0 (61·0–75·0) | 69·0 (60·0–76·0) |
| Sex | | | | | |
| Female | 1332 (23·9%) | 1316 (23·6%) | 2648 (23·7%) | 1440 (23·6%) | 1208 (23·9%) |
| Male | 4247 (76·1%) | 4260 (76·4%) | 8507 (76·3%) | 4665 (76·4%) | 3842 (76·1%) |
| Race* | | | | | |
| White | 3563 (63·9%) | 3610 (64·7%) | 7173 (64·3%) | 3934 (64·4%) | 3239 (64·1%) |
| Black† | 554 (9·9%) | 520 (9·3%) | 1074 (9·6%) | 656 (10·7%) | 418 (8·3%) |
| American Indian or Alaskan | 183 (3·3%) | 170 (3·0%) | 353 (3·2%) | 301 (4·9%) | 52 (1·0%) |
| Native Hawaiian or Pacific Islander | 7 (0·1%) | 18 (0·3%) | 25 (0·2%) | 11 (0·2%) | 14 (0·3%) |
| Asian | 954 (17·1%) | 924 (16·6%) | 1878 (16·8%) | 746 (12·2%) | 1132 (22·4%) |
| Multiracial | 496 (8·9%) | 510 (9·1%) | 1006 (9·0%) | 643 (10·5%) | 363 (7·2%) |
| Not reported | 2 (<0·1%) | 0 | 2 (<0·1%) | 1 (<0·1%) | 1 (<0·1%) |
| Geographical region | | | | | |
| Eastern Europe | 1671 (30·0%) | 1723 (30·9%) | 3394 (30·4%) | 1700 (27·8%) | 1694 (33·5%) |
| Latin and South America | 1250 (22·4%) | 1249 (22·4%) | 2499 (22·4%) | 1775 (29·1%) | 724 (14·3%) |
| Asia–Pacific | 1024 (18·4%) | 1013 (18·2%) | 2037 (18·3%) | 854 (14·0%) | 1183 (23·4%) |
| Western Europe | 1029 (18·4%) | 987 (17·7%) | 2016 (18·1%) | 1127 (18·5%) | 889 (17·6%) |
| North America | 605 (10·8%) | 604 (10·8%) | 1209 (10·8%) | 649 (10·6%) | 560 (11·1%) |
| Comorbidities | | | | | |
| Ischaemic heart disease | 3622 (64·9%) | 3567 (64·0%) | 7189 (64·4%) | 3946 (64·6%) | 3243 (64·2%) |
| Diabetes | 2500 (44·8%) | 2454 (44·0%) | 4954 (44·4%) | 2585 (42·3%) | 2369 (46·9%) |
| Atrial fibrillation | 2233 (40·0%) | 2352 (42·2%) | 4585 (41·1%) | 2317 (38·0%) | 2268 (44·9%) |
| No previous hospitalisation for heart failure | 1426 (25·6%) | 1473 (26·4%) | 2899 (26·0%) | 2899 (47·5%) | 801 (15·9%)‡ |
| BMI (kg/m²) | 27·2 (24·0–31·1) | 27·4 (24·2–31·3) | 27·3 (24·1–31·2) | 27·6 (24·5–31·4) | 26·9 (23·7–30·9) |
| Baseline NT-proBNP concentration (pg/mL) | 1847 (1042–3542) | 1875 (1029–3535) | 1864 (1036–3537) | 1375 (827–2393) | 2816 (1556–5314) |
| NT-proBNP concentration at randomisation§ | | | | | |
| ≤6000 pg/mL | 4787 (85·8%) | 4779 (85·7%) | 9566 (85·8%) | 5784 (94·7%) | 3782 (74·9%) |
| >6000 pg/mL | 626 (11·2%) | 598 (10·7%) | 1224 (11·0%) | 201 (3·3%) | 1023 (20·3%) |
| New York Heart Association class | | | | | |
| I | 0 | 2 (<0·1%) | 2 (<0·1%) | 0 | 2 (<0·1%) |
| II | 3889 (69·7%) | 3908 (70·1%) | 7797 (69·9%) | 4822 (79·0%) | 2975 (58·9%) |
| III–IV | 1687 (30·2%) | 1665 (29·9%) | 3352 (30·0%) | 1283 (21·0%) | 2069 (41·0%) |
| Missing | 3 (<0·1%) | 1 (<0·1%) | 4 (<0·1%) | 0 | 4 (<0·1%) |
| Left ventricular ejection fraction at screening (%) | 29·8% (7·6) | 29·7% (7·7) | 29·8% (7·7) | 30·4% (7·0) | 28·9% (8·3) |
| eGFR (mL/min per 1·73 m²) | 66·6 (25·8) | 66·6 (26·1) | 66·6 (25·9) | 70·9 (24·0) | 61·5 (27·2) |
| eGFR values at randomisation | | | | | |
| <15 mL/min per 1·73 m² | 7 (0·1%) | 12 (0·2%) | 19 (0·2%) | 7 (0·1%) | 12 (0·2%) |
| ≥15 to <30 mL/min per 1·73 m² | 373 (6·7%) | 364 (6·5%) | 737 (6·6%) | 243 (4·0%) | 494 (9·8%) |
| ≥30 to <60 mL/min per 1·73 m² | 1975 (35·4%) | 2004 (35·9%) | 3979 (35·7%) | 1861 (30·5%) | 2118 (41·9%) |
| ≥60 mL/min per 1·73 m² | 3115 (55·8%) | 3095 (55·5%) | 6210 (55·7%) | 3875 (63·5%) | 2335 (46·2%) |
| Missing | 109 (2·0%) | 101 (1·8%) | 210 (1·9%) | 119 (1·9%) | 91 (1·8%) |

(Table 1 continues on next page)

(Continued from previous page)

| | Pooled trials (VICTOR and VICTORIA) | | | VICTOR (n=6105) | VICTORIA (n=5050) |
|---|---|---|---|---|---|
| | Vericiguat (n=5579) | Placebo (n=5576) | Pooled (n=11155) | | |
| Medical therapy | | | | | |
| β blockers | 5235 (93·8%) | 5222 (93·7%) | 10457 (93·7%) | 5766 (94·4%) | 4691 (92·9%) |
| Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker | 2997 (53·7%) | 3041 (54·5%) | 6038 (54·1%) | 2338 (38·3%) | 3700 (73·3%) |
| Sacubitril-valsartan | 2094 (37·5%) | 2053 (36·8%) | 4147 (37·2%) | 3416 (56·0%) | 731 (14·5%) |
| Mineralocorticoid receptor antagonists | 4105 (73·6%) | 4188 (75·1%) | 8293 (74·3%) | 4748 (77·8%) | 3545 (70·2%) |
| SGLT2 inhibitors | 1918 (34·4%) | 1904 (34·1%) | 3822 (34·3%) | 3610 (59·1%) | 212 (4·2%) |
| Device therapy | | | | | |
| Implantable cardioverter-defibrillator | 1689 (30·3%) | 1719 (30·8%) | 3408 (30·6%) | 2009 (32·9%) | 1399 (27·7%) |
| Cardiac resynchronisation therapy | 834 (14·9%) | 809 (14·5%) | 1643 (14·7%) | 904 (14·8%) | 739 (14·6%) |
| Cardiac resynchronisation therapy-defibrillator, or both implantable cardioverter-defibrillator and cardiac resynchronisation therapy | 595 (10·7%) | 605 (10·9%) | 1200 (10·8%) | 677 (11·1%) | 523 (10·4%) |

Data are median (IQR), n (%), or mean (SD). eGFR=estimated glomerular filtration rate. *Numbers for each race category do not sum to the total number of participants because participants could select more than one race. †Includes participants who identify as Black or multiracial including Black. ‡801 participants without previous hospitalisation for heart failure were enrolled into the VICTORIA trial as they had previously received intravenous diuretics. These 801 participants were not included in the pooled columns. §Percentage of participants in the intention-to-treat population for whom baseline NT-proBNP concentrations were available. Data for 365 (3·3%) of 11155 pooled participants were missing: 166 (3·0%) of 5579 participants in the vericiguat group and 199 (3·6%) of 5576 participants in the placebo group. Of the 10790 participants with available data, 9566 (88·7%) of the pooled population had baseline NT-proBNP concentrations of 6000 pg/mL or lower.

*Table 1:* Baseline characteristics of the VICTORIA and VICTOR trials

| | Vericiguat (n=5579) | | Placebo (n=5576) | | Hazard ratio (95% CI)† | p value‡ |
|---|---|---|---|---|---|---|
| | Patients with event | Events per 100 patient-years* | Patients with event | Events per 100 patient-years* | | |
| **Primary outcome** | | | | | | |
| Cardiovascular death or hospitalisation for heart failure | 1446 (25·9%) | 19·3 | 1556 (27·9%) | 21·2 | 0·91 (0·85–0·98) | 0·0088 |
| Cardiovascular death§ | 407 (7·3%) | .. | 447 (8·0%) | .. | .. | .. |
| Hospitalisation for heart failure§ | 1039 (18·6%) | .. | 1109 (19·9%) | .. | .. | .. |
| **Secondary outcomes** | | | | | | |
| Cardiovascular death | 706 (12·7%) | 8·4 | 787 (14·1%) | 9·5 | 0·89 (0·80–0·98) | 0·020 |
| First hospitalisation for heart failure | 1039 (18·6%) | 13·8 | 1109 (19·9%) | 15·1 | 0·92 (0·84–1·00) | 0·043 |
| Total hospitalisations for heart failure (first and recurrent events) | 1772 | 21·3 | 1933 | 23·6 | 0·91 (0·85–0·97) | 0·0050 |
| All-cause death | 889 (15·9%) | 10·6 | 974 (17·5%) | 11·8 | 0·90 (0·82–0·99) | 0·025 |

For participants with multiple events in a composite event outcome, only the first event contributing to the composite endpoint is counted. *Number of participants with an event per 100 patient-years at risk. †Calculated with a Cox proportional hazard model controlling for stratification factors defined by trial. ‡Calculated with a two-sided log-rank test stratified by the stratification factors defined by trial. §Components of the composite primary outcome as first events.

*Table 2:* Efficacy outcomes in the pooled VICTORIA and VICTOR trials population

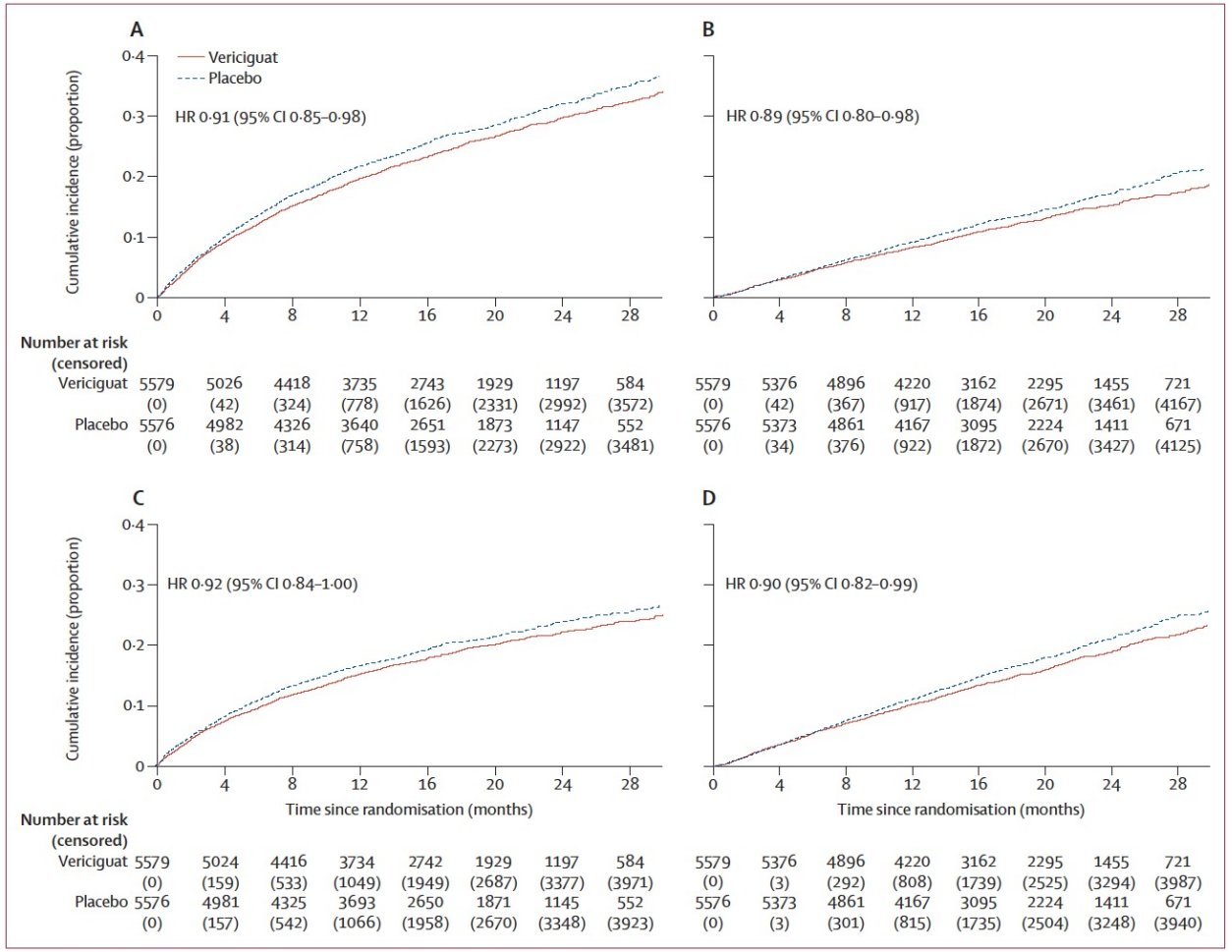



***Figure 2:*** **Kaplan–Meier curves of efficacy outcomes for the pooled population**

(A) Primary composite outcome of cardiovascular death or hospitalisation for heart failure. (B) Cardiovascular death. (C) Hospitalisation for heart failure. (D) All-cause death. HR=hazard ratio.

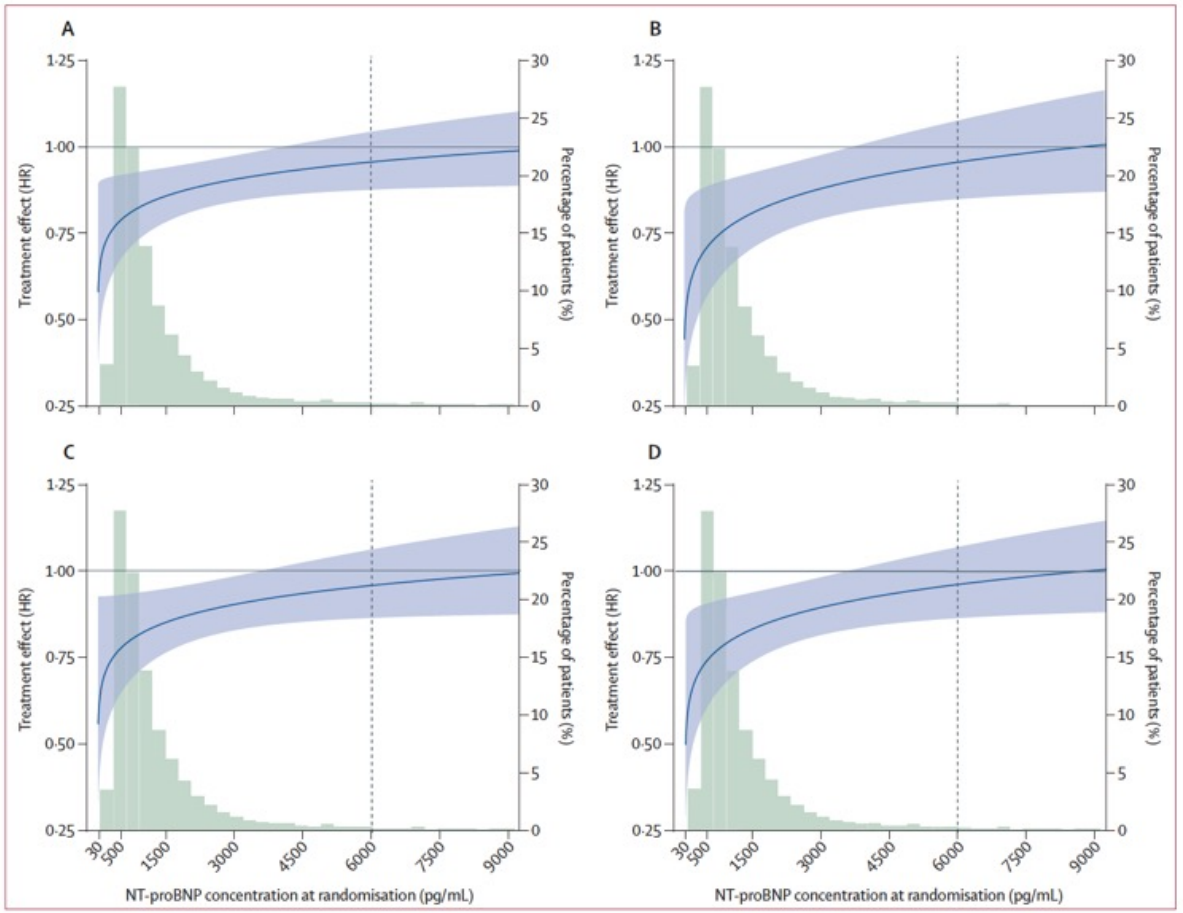



*Figure 3*: **Treatment effects on efficacy outcomes by baseline NT-proBNP concentration**

Treatment effect across the range of NT-proBNP concentrations at randomisation for the primary composite outcome (A), cardiovascular death (B), hospitalisation for heart failure (C), and all-cause death (D). The left-hand y-axis shows the treatment effect, expressed as HR (blue line) with 95% CI (shaded area), adjusted for the trial effect. The right-hand y-axis indicates the percentage of patients, shown by green shaded bars, within each NT-proBNP concentration group. The vertical blue dotted line indicates an NT-proBNP concentration of 6000 pg/mL. The concentrations were obtained from a back-transformation of log-transformed NT-proBNP concentrations. The x-axis is truncated at 10 000 pg/mL for presentation purposes. The entry criteria for the VICTORIA and VICTOR trials differed in terms of baseline NT-proBNP concentrations: >1000 pg/mL for the VICTORIA trial and 600–6000 pg/mL in the VICTOR trial, with higher minimum thresholds in both trials if patients had atrial fibrillation at screening. HR=hazard ratio.

## Research in context

### Evidence before this study

We searched PubMed from database inception to July 28, 2025, using the search terms "heart failure" and "vericiguat", for English-language publications reporting studies in humans. This search identified 237 records, one of which reported a randomised controlled trial (VICTORIA) with adjudicated endpoints in a population with heart failure and reduced ejection fraction (HFrEF). In the VICTORIA trial, vericiguat reduced the risk of cardiovascular death or hospitalisation for heart failure in patients with HFrEF with recent worsening (defined as either a hospitalisation for heart failure within the previous 6 months or outpatient use of intravenous diuretics within the previous 3 months). On the basis of this trial, vericiguat was approved for the treatment of patients with worsening HFrEF and received a class IIb recommendation in European and North American guidelines. The median mortality follow-up in VICTORIA was 13·7 months, which limited the ability to assess the effects of longer-term exposure to vericiguat on cardiovascular death. The use of angiotensin receptor–neprilysin inhibitors and sodium–glucose cotransporter 2 inhibitors was low, consistent with standard practice during the enrolment period of 2016–18. In addition, patients with baseline NT-proBNP concentrations in the upper quartile (>5314 pg/mL) accrued less benefit from vericiguat than did those with NT-proBNP concentrations in the lower three quartiles. The VICTOR trial, which enrolled patients from 2021 to 2023, was designed to complement the VICTORIA trial by assessing the efficacy of vericiguat in patients with HFrEF and no recent worsening, a more contemporary heart failure background therapy, and a baseline NT-proBNP concentration of 6000 pg/mL or lower. Vericiguat did not reduce the primary composite endpoint of cardiovascular death or hospitalisation for heart failure. However, the trial was also powered to assess the effect of vericiguat on cardiovascular death, and significantly fewer cardiovascular deaths were observed among patients who received vericiguat than among those who received placebo.

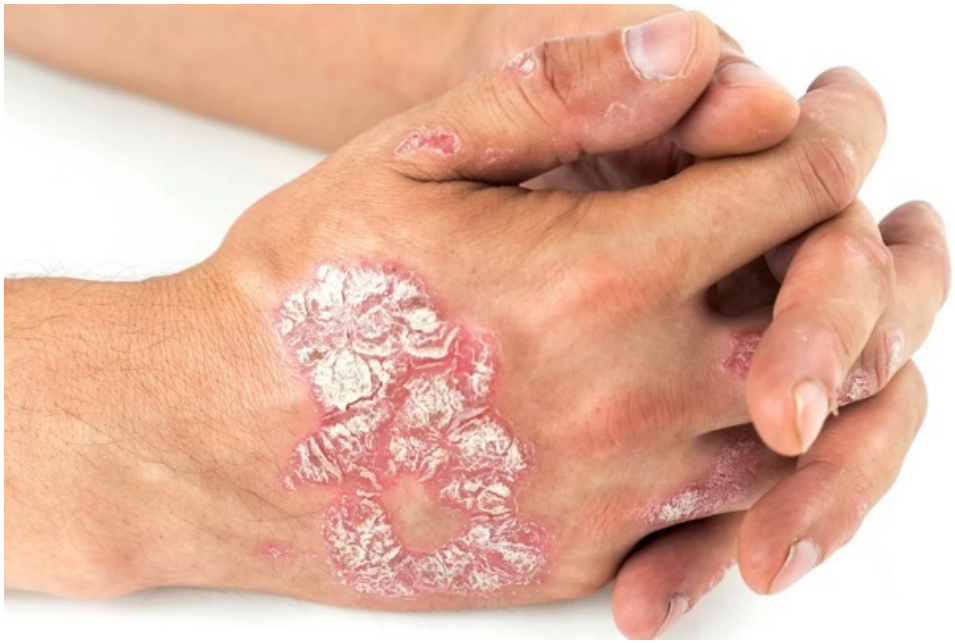
### Added value of this study

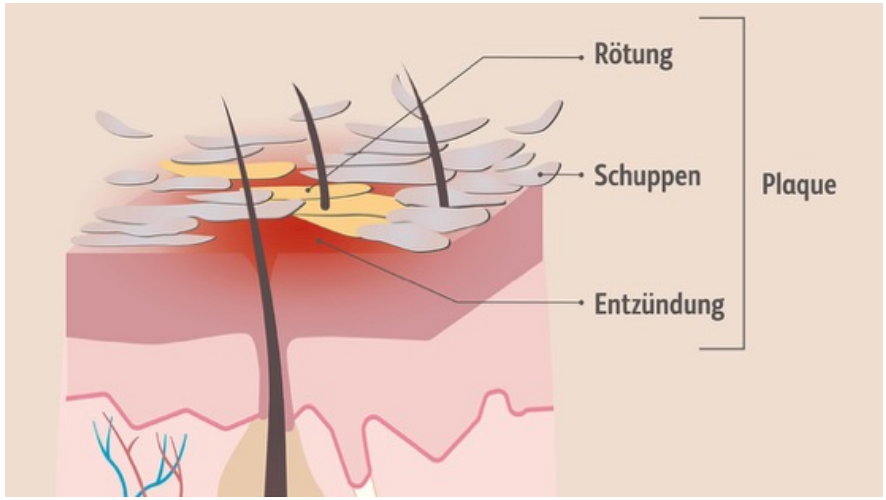
This pooled, participant-level analysis of two large outcomes trials of vericiguat included patients with HFrEF across a broad range of clinical severity. We found that treatment with vericiguat reduced the composite endpoint of cardiovascular death and hospitalisation for heart failure, the individual components alone, and all-cause death, with no evidence of intertrial heterogeneity of the treatment effect. The benefit of vericiguat appeared greater in the large cohort of patients with an NT-proBNP concentration of 6000 pg/mL or lower.

### Implications of all the available evidence

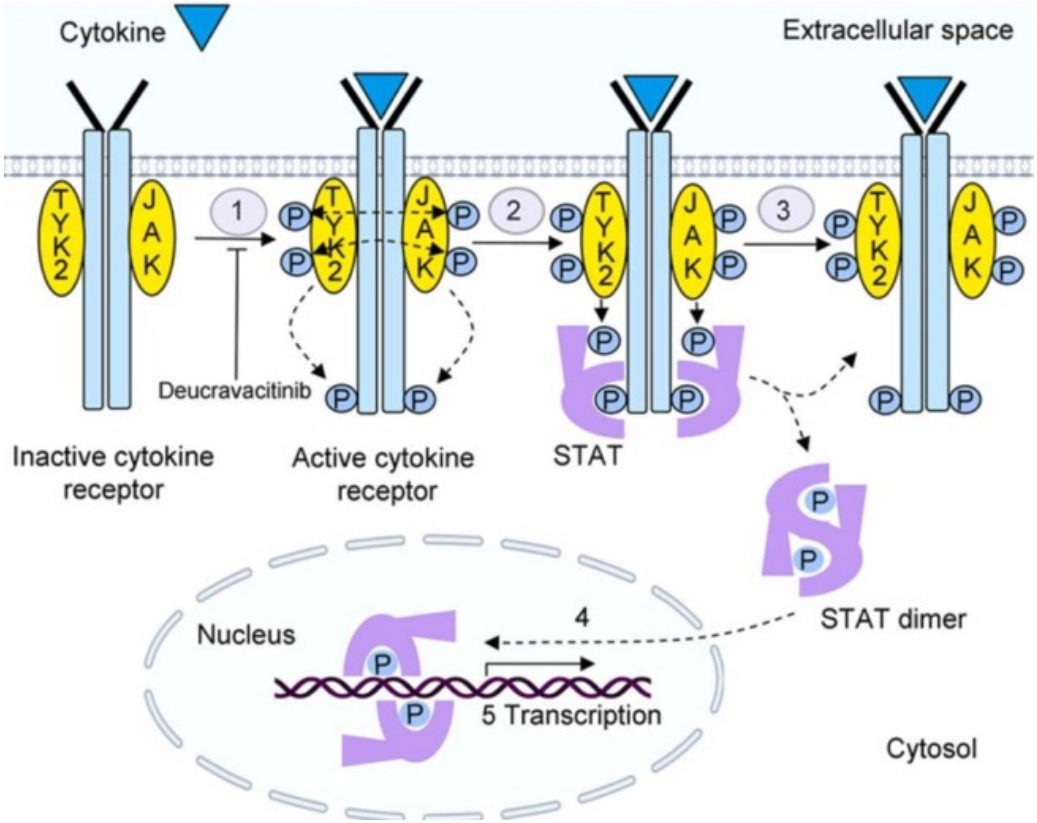
The once-daily administration and favourable tolerability and safety profile of vericiguat support its consideration as an additional therapeutic option for patients with HFrEF, particularly those with recent worsening (as demonstrated in the VICTORIA trial). In the VICTOR trial, vericiguat did not reduce the risk of the primary composite endpoint of cardiovascular death or hospitalisation for heart failure; however, vericiguat was associated with a reduction in cardiovascular and all-cause mortality in stable ambulatory patients with HFrEF. These findings suggest that vericiguat might offer clinical benefit in selected patient populations across the spectrum of HFrEF. Further research is warranted to clarify its optimal role in the management of ambulatory patients.

Plaque-Psoriasis, die häufigste Form der Schuppenflechte, ist eine Autoimmunerkrankung, die zu scharf begrenzten, roten, erhabenen Hautstellen, den Plaques, führt, die mit silbrig-weißen Schuppen bedeckt sind und jucken, schmerzen oder brennen können. Die Erkrankung entsteht durch eine Überreaktion des Immunsystems, die zu einer beschleunigten Hautzellbildung führt, und kann überall am Körper auftreten, am häufigsten an Ellenbogen, Knien und Kopfhaut. Neben Hautreaktionen können auch Nägel, Gelenke (Psoriasis-Arthritis) und das Herz-Kreislauf-System betroffen sein, wobei Stress, Infektionen und bestimmte Medikamente Auslöser für Schübe sein können.

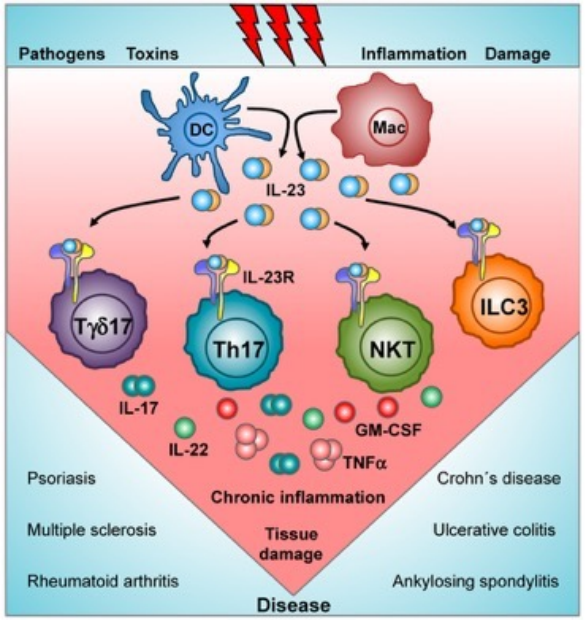


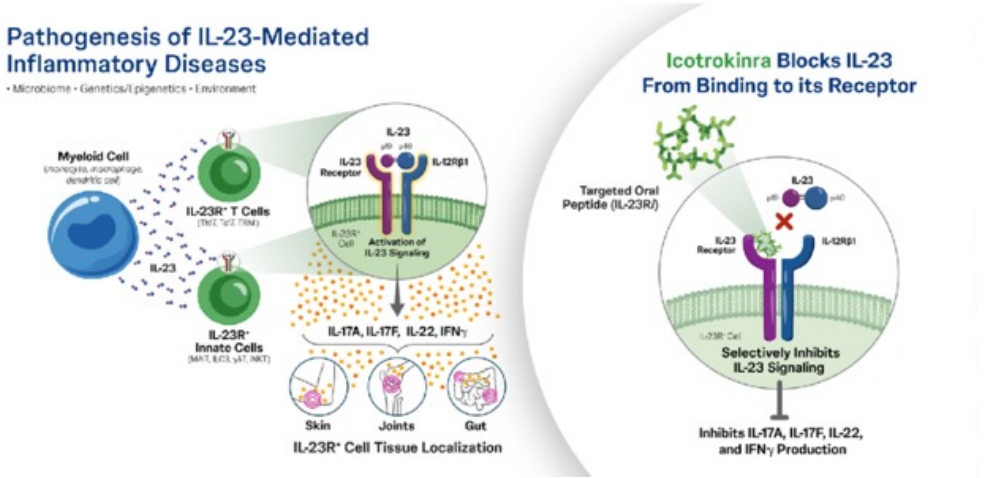


Deucravacitinib ist der Wirkstoffname für Sotyktu, ein Medikament zur Behandlung von mittelschwerer bis schwerer Plaque-Psoriasis bei Erwachsenen. Als Tyrosinkinasehemmer der sogenannten JAK-Inhibitoren-Klasse wirkt es, indem es gezielt die Aktivität der Januskinase TYK2 hemmt und so die entzündungsfördernden Signalwege unterbricht, die bei Psoriasis eine Rolle spielen. Das Medikament ist als Filmtabletten zur täglichen Einnahme konzipiert und wird über den Mund (oral) verabreicht.



Icotrokinra ist ein Wirkstoff, der später einmal in einem Medikament zum Einsatz kommen soll. Er blockiert gezielt den IL-23-Rezeptor. Dieser Rezeptor spielt eine wichtige Rolle bei der Entstehung von Psoriasis. Das Medikament wird als Tablette eingenommen.



# Once-daily oral icotrokinra versus placebo and once-daily oral deucravacitinib in participants with moderate-to-severe plaque psoriasis (ICONIC-ADVANCE 1 & 2): two phase 3, randomised, placebo-controlled and active-comparator-controlled trials


## Summary

**Background** Monoclonal antibodies targeting interleukin-23 and interleukin-12 are efficacious in treating plaque psoriasis but must be delivered via intravenous or subcutaneous injection. Here, we aimed to evaluate the efficacy and safety of icotrokinra (JNJ-77242113), a targeted oral peptide that selectively binds the interleukin-23 receptor, compared with both placebo and deucravacitinib in adults with moderate-to-severe plaque psoriasis.

**Methods** The phase 3, randomised, double-blind, placebo-controlled and active-comparator-controlled ICONIC-ADVANCE 1 and ICONIC-ADVANCE 2 trials, which are being done at 149 sites across 13 countries and 114 sites across 11 countries, respectively, randomly assigned (2:1:2 and 4:1:4, respectively) adults with moderate-to-severe plaque psoriasis diagnosed for at least 26 weeks (body-surface-area involvement ≥10%, Psoriasis Area and Severity Index [PASI] ≥12, and Investigator's Global Assessment [IGA] ≥3) to once-daily oral icotrokinra 200 mg, placebo, or deucravacitinib 6 mg; participants randomly assigned to placebo or deucravacitinib transitioned to icotrokinra at week 16 or week 24, respectively. Coprimary endpoints were proportions of participants achieving IGA 0 or 1 (clear or almost clear skin) with at least a two-grade improvement and at least 90% improvement in PASI (PASI 90) at week 16 with icotrokinra versus placebo. These studies are registered with ClinicalTrials.gov, NCT06143878 (ADVANCE 1) and NCT06220604 (ADVANCE 2), and are ongoing.

**Findings** ICONIC-ADVANCE 1 enrolled participants from Jan 17, 2024, to May 24, 2024, and ICONIC-ADVANCE 2 enrolled participants from March 9, 2024, to June 13, 2024. Participants (ADVANCE 1: 774 of 988 patients screened; ADVANCE 2: 731 of 917 patients screened) were randomly assigned to icotrokinra (n=311 and 322), placebo (n=156 and 82), or deucravacitinib (n=307 and 327). All coprimary endpoints were met in both trials. Higher proportions of icotrokinra-treated versus placebo-treated participants achieved IGA 0 or 1 (ADVANCE 1: 213 [68%] of 311 *vs* 17 [11%] of 156, treatment difference 95% CI 58% [50–64]; ADVANCE 2: 227 [70%] of 322 *vs* seven [9%] of 82, 62% [53–69]; both p<0·0001) and PASI 90 (ADVANCE 1: 171 [55%] of 311 *vs* six [4%] of 156, treatment difference 95% CI 51% [44–57]; ADVANCE 2: 184 [57%] of 322 *vs* one [1%] of 82, 56% [48–62]; both p<0·0001) at week 16. Across studies, adverse event rates to week 16 were 303 (48%) of 632 and 136 (57%) of 237 with icotrokinra and placebo, respectively; the most common adverse events were nasopharyngitis (37 [6%] of 632 and 13 [5%] of 237) and upper respiratory tract infection (23 [4%] of 632 and eight [3%] of 237). To week 24, adverse event rates were lower than with icotrokinra (359 [57%] of 632) than deucravacitinib (411 [65%] of 634).

**Interpretation** Icotrokinra showed superior clinical response rates versus placebo and deucravacitinib in phase 3 moderate-to-severe plaque psoriasis trials, with similar adverse event rates to placebo. These findings suggest the potential of once-daily oral icotrokinra to provide robust efficacy and a favourable safety profile.

| | ICONIC-ADVANCE 1 | | | ICONIC-ADVANCE 2 | | |
|---|---|---|---|---|---|---|
| | Icotrokinra (n=311) | Placebo (n=156) | Deucravacitinib (n=307) | Icotrokinra (n=322) | Placebo (n=82) | Deucravacitinib (n=327) |
| **Demographics** | | | | | | |
| Age, years | 47·1 (13·19) | 46·9 (12·78) | 46·3 (13·87) | 45·9 (13·78) | 48·4 (13·90) | 45·6 (13·22) |
| Sex | | | | | | |
| Female | 88 (28%) | 51 (33%) | 107 (35%) | 104 (32%) | 27 (33%) | 104 (32%) |
| Male | 223 (72%) | 105 (67%) | 200 (65%) | 218 (68%) | 55 (67%) | 223 (68%) |
| Race or ethnic group | | | | | | |
| American Indian or Alaska Native | 1 (<1%) | 1 (<1%) | 1 (<1%) | 1 (<1%) | 0 | 1 (<1%) |
| Asian | 69 (22%) | 34 (22%) | 77 (25%) | 34 (11%) | 15 (18%) | 40 (12%) |
| Black | 4 (1%) | 3 (2%) | 4 (1%) | 9 (3%) | 2 (2%) | 11 (3%) |
| Native Hawaiian or other Pacific Islander | 2 (1%) | 0 | 0 | 2 (1%) | 0 | 3 (1%) |
| White | 231 (74%) | 118 (76%) | 221 (72%) | 274 (85%) | 65 (79%) | 265 (81%) |
| Unknown or not reported | 4 (1%) | 0 | 4 (1%) | 1 (<1%) | 0 | 5 (2%) |
| Ethnicity | | | | | | |
| Hispanic or Latinx | 58 (19%) | 25 (16%) | 49 (16%) | 42 (13%) | 12 (15%) | 48 (15%) |
| Not Hispanic or Latinx | 250 (80%) | 129 (83%) | 257 (84%) | 279 (87%) | 70 (85%) | 279 (85%) |
| Unknown or not reported | 3 (1%) | 2 (1%) | 1 (<1) | 1 (<1%) | 0 | 0 |
| Weight, kg | 86·9 (21·08) | 88·2 (25·08) | 87·7 (23·04) | 88·8 (20·12) | 86·4 (18·84) | 89·8 (21·43) |
| BMI,* kg/m² | 29·2 (6·31) | 29·6 (8·08) | 29·9 (7·28) | 29·9 (6·36) | 29·5 (5·78) | 29·9 (6·86) |
| **Disease characteristics** | | | | | | |
| Age at psoriasis diagnosis, years | 29·7 (14·81) | 29·1 (16·13) | 29·6 (15·21) | 28·6 (15·69) | 27·3 (16·23) | 28·9 (14·63) |
| Duration of psoriasis, years | 17·52 (11·10) | 17·88 (12·75) | 16·81 (12·81) | 17·43 (13·38) | 21·21 (15·17) | 16·82 (12·03) |
| Psoriasis Area and Severity Index total score (0–72) | 18·60 (15·50–22·70) | 17·15 (14·40–21·65) | 18·00 (15·00–23·40) | 18·00 (15·10–22·20) | 17·95 (14·30–23·60) | 17·60 (15·20–21·40) |
| Percentage of BSA* | 20·00% (16·00–32·00) | 20·00% (14·00–30·75) | 21·00% (14·00–34·00) | 21·00% (15·00–32·00) | 22·00% (15·00–33·00) | 20·00% (15·50–32·00) |
| Investigator's Global Assessment score | | | | | | |
| 3 (moderate) | 251 (81%) | 123 (79%) | 242 (79%) | 252 (78%) | 67 (82%) | 267 (82%) |
| 4 (severe) | 60 (19%) | 33 (21%) | 65 (21%) | 70 (22%) | 15 (18%) | 60 (18%) |
| Scalp-specific Investigator's Global Assessment score† | | | | | | |
| 2 (mild) | 45 (14%) | 30 (19%) | 55 (18%) | 62 (19%) | 17 (21%) | 62 (19%) |
| 3 (moderate) | 177 (57%) | 85 (54%) | 166 (54%) | 169 (52%) | 48 (59%) | 176 (54%) |
| 4 (severe) | 39 (13%) | 19 (12%) | 47 (15%) | 39 (12%) | 6 (7%) | 40 (12%) |
| PSSD Symptom score‡ (1–100) | 50·0 (28·0–70·0) | 44·0 (24·0–68·0) | 52·0 (30·0–70·0) | 54·0 (30·0–76·0) | 52·0 (32·0–74·0) | 57·0 (32·0–76·0) |
| PSSD Sign score‡ (1–100) | 57·0 (42·0–73·0) | 51·0 (33·0–68·0) | 57·0 (38·0–73·0) | 60·0 (38·0–77·0) | 55·0 (42·0–77·0) | 63·0 (45·0–77·0) |
| PSSD Itch score‡ | 7·0 (5·0–8·0) | 6·0 (4·0–8·0) | 7·0 (5·0–8·0) | 7·0 (5·0–8·0) | 7·0 (4·0–8·0) | 7·0 (5·0–8·0) |
| **Previous psoriasis therapy** | | | | | | |
| Systemic therapy§ | 236 (76%) | 110 (71%) | 225 (73%) | 225 (70%) | 58 (71%) | 230 (70%) |
| Phototherapy¶ | 112 (36%) | 53 (34%) | 97 (32%) | 98 (30%) | 31 (38%) | 109 (33%) |
| Conventional non-biological systemic therapy‖ | 171 (55%) | 79 (51%) | 152 (50%) | 165 (51%) | 39 (48%) | 163 (50%) |
| Novel non-biological systemic therapy** | 22 (7%) | 12 (8%) | 38 (12%) | 16 (5%) | 3 (4%) | 12 (4%) |
| Biological therapy†† | 86 (28%) | 42 (27%) | 80 (26%) | 78 (24%) | 26 (32%) | 77 (24%) |

Data are n (%), mean (SD), or median (IQR) unless otherwise noted. Percentages may not total 100 because of rounding. BSA=body surface area. PSSD=Psoriasis Symptoms and Signs Diary. PUVA=psoralen and long-wave ultraviolet light. UVB=short wave ultraviolet light. *Among 322 participants in the icotrokinra group, 82 in the placebo group, and 325 in the deucravacitinib group in ICONIC-ADVANCE 2. †Among 308 participants in the icotrokinra group, 156 in the placebo group, and 306 in the deucravacitinib group in ICONIC-ADVANCE 1 and 321, 82, and 324 participants, respectively, in ICONIC-ADVANCE 2. ‡Among 287 participants in the icotrokinra group, 142 in the placebo group, and 277 in the deucravacitinib group in ICONIC-ADVANCE 1 and 299, 71, and 290 participants, respectively, in ICONIC-ADVANCE 2. §Includes conventional non-biological systemics, novel non-biological systemics, 1,25-vitamin D3 and analogues, phototherapy, and biologics. ¶Includes PUVA and UVB. ‖Includes PUVA, methotrexate, cyclosporine, acitretin, azathioprine, and fumarate. **Includes apremilast and tofacitinib. ††Includes etanercept, infliximab, adalimumab, ustekinumab, briakinumab, secukinumab, ixekizumab, brodalumab, guselkumab, risankizumab, tildrakizumab, alefacept, efalizumab, natalizumab, and certolizumab pegol.

*Table 1:* Demographics and baseline clinical characteristics

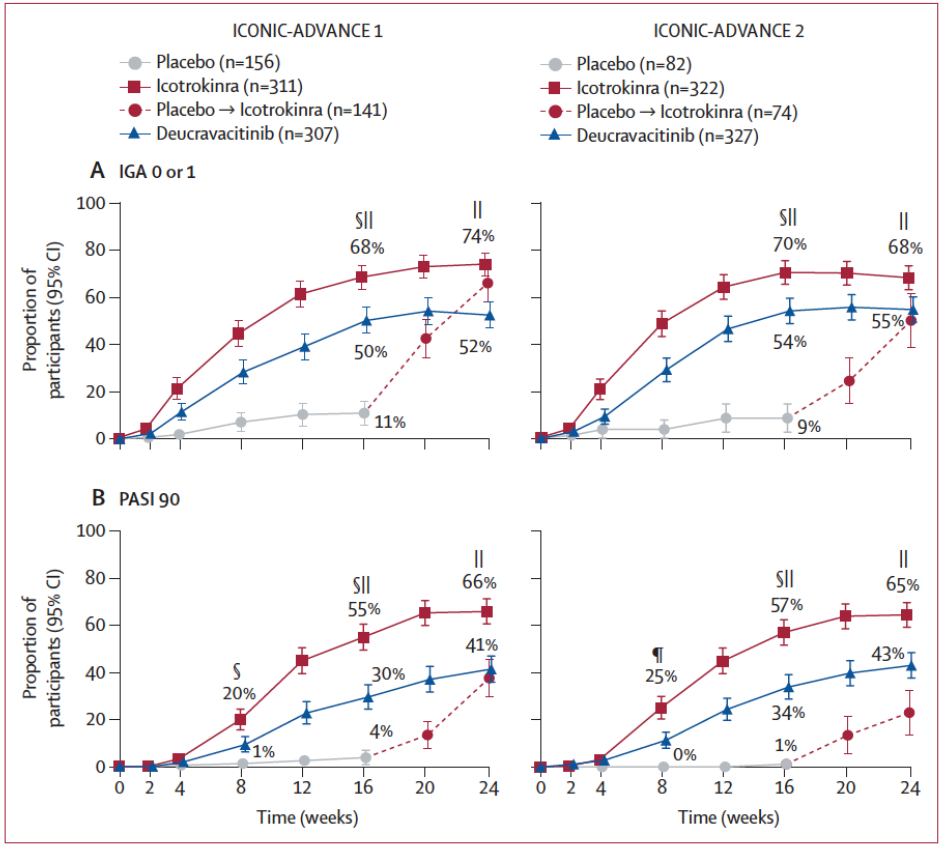



***Figure 2:*** **Proportions of participants achieving the coprimary endpoints of IGA 0 or 1* and PASI 90 by treatment group over time†‡**

IGA=Investigator's Global Assessment. PASI=Psoriasis Area and Severity Index. *With a ≥2-grade improvement from baseline. †In ICONIC-ADVANCE 1, the rates of participants with missing IGA or PASI data at week 16 were five (3%) of 156, 14 (4%) of 311, and 15 (5%) of 307 for the placebo, icotrokinra, and deucravacitinib groups, respectively. ‡In ICONIC-ADVANCE 2, the rates of participants with missing IGA or PASI data at week 16 were four (5%) of 82, 11 (3%) of 322, and 11 (3%) of 327 for the placebo, icotrokinra, and deucravacitinib groups, respectively. §Multiplicity-adjusted p<0·001, icotrokinra versus placebo. ¶Multiplicity-adjusted p<0·01, icotrokinra versus placebo. ||Multiplicity-adjusted p<0·001, icotrokinra versus deucravacitinib. Error bars represent 95% CI.

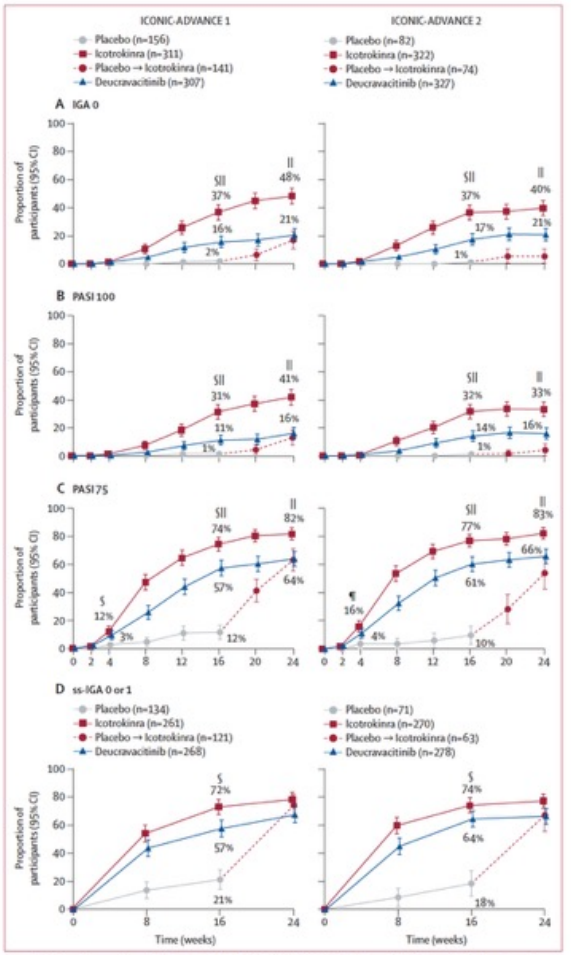



***Figure 3:*** **Proportions of participants achieving IGA 0, PASI 100, PASI 75, and ss-IGA 0 or 1* by treatment group over time†‡**

IGA=Investigator's Global Assessment. PASI=Psoriasis Area and Severity Index. ss-IGA=scalp-specific Investigator's Global Assessment. *With a ≥2-grade improvement from baseline. †In ICONIC-ADVANCE 1, the rates of participants with missing IGA or PASI data at week 16 were 3% (5 of 156), 4% (14 of 311), and 5% (15 of 307) for the placebo, icotrokinra, and deucravacitinib groups, respectively. ‡In ICONIC-ADVANCE 2, the rates of participants with missing IGA or PASI data at week 16 were 5% (four of 82), 3% (11 of 322), and 3% (11 of 327) for the placebo, icotrokinra, and deucravacitinib groups, respectively. §Multiplicity-adjusted p<0·001, icotrokinra versus placebo. ¶Multiplicity-adjusted p<0·01, icotrokinra versus placebo. ‖Multiplicity-adjusted p<0·001, icotrokinra versus deucravacitinib. Error bars represent 95% CI.

| | Placebo-controlled (weeks 0–16) | | | Active-comparator controlled (weeks 0–24) | | Crossover (weeks 16–24) |
|---|---|---|---|---|---|---|
| | Icotrokinra | Placebo | Deucravacitinib | Icotrokinra | Deucravacitinib | Placebo→icotrokinra |
| Number of participants | 632 | 237 | 634 | 632 | 634 | 215 |
| Mean weeks of follow-up (SD) | 15·9 (1·88) | 15·5 (2·69) | 15·8 (2·25) | 23·5 (3·26) | 23·3 (3·94) | 8·1 (0·58) |
| ≥1 adverse event | 303 (48%) | 136 (57%) | 360 (57%) | 359 (57%) | 411 (65%) | 60 (28%) |
| Adverse events occurring in ≥5% of participants† | | | | | | |
| Headache | 26 (4%) | 11 (5%) | 19 (3%) | 28 (4%) | 20 (3%) | 3 (1%) |
| Nasopharyngitis | 37 (6%) | 13 (5%) | 58 (9%) | 56 (9%) | 77 (12%) | 8 (4%) |
| Upper respiratory tract infection | 23 (4%) | 8 (3%) | 33 (5%) | 32 (5%) | 49 (8%) | 7 (3%) |
| Serious adverse event | 14 (2%) | 4 (2%) | 14 (2%) | 18 (3%) | 20 (3%) | 3 (1%) |
| Serious infection‡ | 1 (<1%) | 1 (<1%) | 4 (1%) | 3 (<1%) | 4 (1%) | 0 |
| Adverse event resulting in discontinuation | 13 (2%) | 12 (5%) | 14 (2%) | 15 (2%) | 17 (3%) | 0 |
| Gastrointestinal adverse event | 45 (7%) | 15 (6%) | 63 (10%) | 55 (9%) | 80 (13%) | 5 (2%) |
| Malignancy§ | 3 (<1%) | 1 (<1%) | 1 (<1%) | 3 (<1%) | 2 (<1%) | 0 |
| Active tuberculosis | 0 | 0 | 0 | 0 | 0 | 0 |

Values are n (%) unless otherwise noted. *The safety analysis set included all randomly assigned and treated participants. †In any treatment group. ‡Serious infections included bacterial arthritis (placebo group), campylobacter colitis (deucravacitinib group), viral infection (deucravacitinib group), infection exacerbated by chronic obstructive airways disease (icotrokinra group), lower respiratory tract infection (deucravacitinib group), viral upper respiratory tract infection (deucravacitinib group), and pneumonia (icotrokinra group). §Details on malignancies reported through week 24 of both studies are provided in the appendix (pp 2–3).

***Table 2:*** **Combined adverse events from the ICONIC-ADVANCE 1 and ICONIC-ADVANCE 2 safety analysis sets***

## Research in context

### Evidence before this study

We searched PubMed for articles published before March 24, 2025, using the terms "psoriasis" and "oral" and "interleukin-23 or IL-23" in their title or abstract with clinical trials as the article type. The search identified 28 articles, of which three described randomised, controlled, phase 3 clinical trials in patients with plaque psoriasis; these studies used an oral therapy (fumaric acid esters or methotrexate) as an active comparator for an injectable IL-23 inhibitor, and all concluded that the injectable IL-23 inhibitor had greater efficacy than the oral comparator. Monoclonal antibodies targeting IL-23 or IL-12/23 (eg, guselkumab, tildrakizumab, risankizumab, and ustekinumab), which are delivered via subcutaneous injection, generally have shown efficacy in treating psoriasis and exhibit safety profiles that are considered favourable compared with conventional systemic therapies. A PubMed search for articles published before March 24, 2025, which used "icotrokinra" or "JNJ-77242113" and "psoriasis" in their title or abstract with clinical trials as the article type, identified two articles, both of which report data from phase 2 studies of icotrokinra (an IL-23 receptor-targeting oral peptide) in patients with moderate-to-severe plaque psoriasis. These studies reported rates of clear or almost clear skin that were higher in patients treated with icotrokinra compared with placebo and were within the range of response rates seen with biological, injectable inhibitors of the IL-23 p19 subunit currently approved to treat psoriasis, with a safety profile similar to placebo. A PubMed search for articles published before March 24, 2025, which used "deucravacitinib" and "apremilast" in their title or abstract with clinical trials as the article type, identified nine articles, all of which report data from phase 3 studies of deucravacitinib (an oral tyrosine kinase 2 [TYK2] inhibitor) versus apremilast (an oral phosphodiesterase 4 inhibitor) in patients with moderate-to-severe plaque psoriasis. Deucravacitinib has shown superior efficacy in treating psoriasis compared with apremilast and is generally well tolerated in adults with moderate-to-severe plaque psoriasis. Therefore, deucravacitinib was selected as the active comparator as it was the most efficacious approved advanced oral medication for the treatment of moderate-to-severe plaque psoriasis.

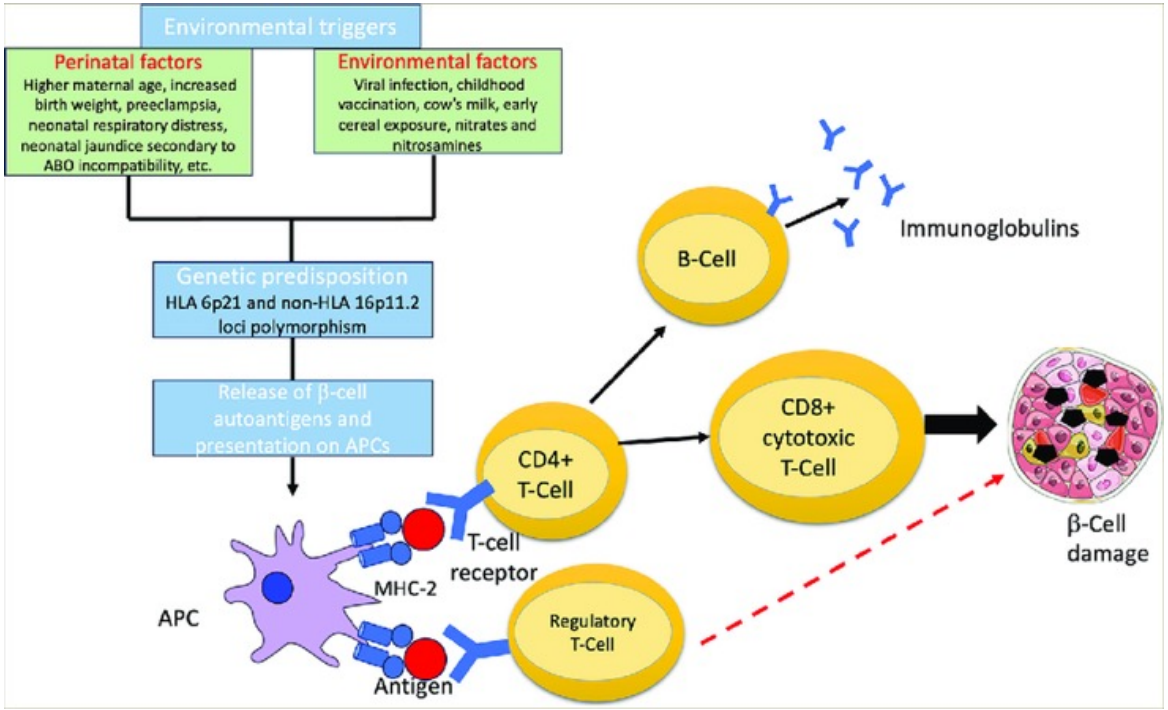
### Added value of this study

ICONIC-ADVANCE 1 and ICONIC-ADVANCE 2 evaluated the efficacy and safety of icotrokinra compared with placebo and deucravacitinib in patients with moderate-to-severe plaque psoriasis. As such, they are the first head-to-head studies comparing an IL-23 receptor-targeting oral peptide with an active comparator, deucravacitinib, an oral TYK2 inhibitor. Across both studies, icotrokinra showed superior skin clearance versus placebo and deucravacitinib for all coprimary and key secondary endpoints. The safety profile of icotrokinra was similar to placebo across both studies.

### Implications of all the available evidence

Data from the placebo-controlled phases of ICONIC-ADVANCE 1 and ICONIC-ADVANCE 2 are consistent with the findings from recently presented phase 3, randomised, controlled studies in which icotrokinra showed superior skin clearance across multiple clinical outcomes, compared with placebo, and a favourable safety profile in adults and adolescents with moderate-to-severe plaque psoriasis (ICONIC-LEAD) and in those with plaque psoriasis involving high-impact sites (ICONIC-TOTAL). Selective blockade of the IL-23 receptor with the targeted oral peptide icotrokinra showed superior skin clearance to placebo and deucravacitinib in two phase 3 trials for moderate-to-severe plaque psoriasis. Up to 16 weeks of treatment, the safety profile of icotrokinra was similar to placebo. These data suggest that once-daily oral icotrokinra can provide robust efficacy and a favourable safety profile for patients with plaque psoriasis.

Type 1 diabetes (T1D) is an autoimmune disease caused by the immune system attacking and destroying insulin-producing beta cells in the pancreas, leading to an absolute or near-absolute lack of insulin and high blood glucose (hyperglycemia). The pathogenesis involves a combination of genetic susceptibility and environmental triggers that break down immune tolerance, resulting in inflammation within the pancreatic islets (insulitis) and progressive beta cell loss. This autoimmune process progresses in stages over time, with autoantibodies appearing before symptoms, leading to the clinical diagnosis of diabetes only after a substantial portion of beta cells have been destroyed.



The efficacy of **antithymocyte globulin (ATG)** in type 1 diabetes has produced mixed results, with some studies showing modest benefits in preserving beta-cell function, especially with low-dose regimens, but overall limited long-term efficacy in most clinical trials.

- **Low-dose ATG (2.5 mg/kg)** has shown potential to **preserve C-peptide levels** (a marker of beta-cell function) and **reduce HbA1c** in new-onset, stage 3 type 1 diabetes, with some patients maintaining near-normal glycemic control and robust C-peptide for several years after treatment. In a small cohort, 50% of children treated with low-dose ATG did not progress to clinical diabetes over follow-up periods of up to four years, and those who did progress still exhibited favorable metabolic control.
- Larger, randomized controlled trials using **standard-dose rabbit ATG (6.5 mg/kg)** in recent-onset type 1 diabetes have generally **not demonstrated significant long-term preservation of beta-cell function** compared to placebo. These studies observed a **biphasic response**: an initial decline in beta-cell function, possibly due to immune activation and side effects like cytokine release syndrome (CRS) and serum sickness, followed by transient stabilization, but ultimately no sustained benefit at 12 or 24 months.
- Some **age-dependent effects** have been reported, with older participants (ages 22–35) showing relative stabilization in C-peptide responses at 12 and 24 months, though these findings were not consistent across all age groups.
- Combination therapies (ATG with G-CSF and/or cyclophosphamide) have shown greater efficacy in pilot studies, with some patients able to discontinue insulin for extended periods, but these regimens involved higher risk and more side effect.
- **Safety**: ATG treatment can cause immune-related adverse events (CRS, serum sickness) but no serious long-term adverse events were reported in low-dose studies. Infectious risk appears low in well-monitored cohorts

# Minimum effective low dose of antithymocyte globulin in people aged 5–25 years with recent-onset stage 3 type 1 diabetes (MELD-ATG): a phase 2, multicentre, double-blind, randomised, placebo-controlled, adaptive dose-ranging trial


## Summary

**Background** Type 1 diabetes remains an important health-care problem, with no disease-modifying therapies available in people with recent-onset, clinical type 1 diabetes. Adaptive trial designs, allowing faster evaluation of treatment modalities, remain underexplored in this stage of the disease. We aimed to identify the minimum effective dose of antithymocyte globulin (ATG) in people aged 5–25 years with recent-onset, clinical type 1 diabetes.

**Methods** MELD-ATG was a phase 2, double-blind, randomised, placebo-controlled, multi-arm, adaptive dose-ranging, parallel-cohort trial done in 14 accredited trial centres in eight countries (the UK, Denmark, Germany, Finland, Italy, Belgium, Austria, and Slovenia). Participants aged 5–25 years, diagnosed with clinical, stage 3 type 1 diabetes 3–9 weeks before treatment, with random C-peptide concentrations 0·2 nmol/L or more and at least one diabetes-related autoantibody (GADA, IA-2A, or ZnT8) were randomly assigned by a web-based randomisation system into seven consecutive cohorts receiving placebo, 2·5 mg/kg ATG, 1·5 mg/kg ATG, 0·5 mg/kg ATG, or 0·1 mg/kg ATG. Participants in cohort 1 were randomly assigned 1:1:1:1:1, participants in cohorts 2 and 3 were randomly assigned 1:1:1:1, and participants in cohorts 4–7 were randomly assigned 1:1:1. All cohorts included one placebo group and one 2·5 mg/kg ATG group. The other groups were assigned to ATG doses that were determined based on accruing data and the decision of the dose determining committee. The trial cohorts were stratified by age group (5–9 years, 10–17 years, and 18–25 years) with block sizes varying by cohort. Concealment lists, outlining the treatment allocation, were only available for the pharmacists; participants and study teams were masked to treatment allocation. ATG was administered by an intravenous infusion over 2 consecutive days. The primary outcome was the area under the curve (AUC) of the stimulated C-peptide concentration during a 2-h mixed-meal tolerance test at 12 months measured as ln(AUC C-peptide+1). Conditional on finding a statistically significant difference at $p<0·05$ for 2·5 mg/kg ATG versus placebo, the minimum effective dose of ATG was determined. All randomly assigned participants were included in the primary analysis. All participants who received the study drug were included in the safety analysis. The trial was registered at ClinicalTrials.gov (NCT04509791) and is completed.

**Findings** Between Nov 24, 2020, and Dec 13, 2023, 152 people were recruited and screened, 117 of whom were randomly assigned (placebo n=31, 0·1 mg/kg ATG n=6, 0·5 mg/kg ATG n=35, 1·5 mg/kg ATG n=12, and 2·5 mg/kg n=33). 54 (46%) of 117 participants were male and 63 (54%) were female. Participants were mainly European. The 0·1 mg/kg dose and the 1·5 mg/kg dose were progressively dropped from the study. At 12 months, the mean ln(AUC C-peptide+1) was 0·411 nmol/L per min (SD 0·032) in the placebo group and 0·535 nmol/L per min (0·032) in the 2·5 mg/kg ATG group. The mean difference in the ln(AUC C-peptide+1) between 2·5 mg/kg ATG and placebo was 0·124 nmol/L per min (95% CI 0·043–0·205; p=0·0028). At 12 months, the mean ln(AUC C-peptide+1) in the 0·5 mg/kg ATG group, the remaining middle dose, was 0·513 nmol/L per min (SD 0·032), with a mean baseline-adjusted difference from placebo of 0·102 nmol/L per min (95% CI 0·021–0·183; p=0·014). Cytokine release syndrome occurred in 11 (33%) of 33 participants in the 2·5 mg/kg ATG group, eight (24%) of 34 in the 0·5mg/kg ATG group, and no participants in the placebo group. Serum sickness occurred in 27 (82%) participants in the 2·5 mg/kg ATG group, 11 (32%) in the 0·5 mg/kg ATG group, and no participants in the placebo group. There were no deaths related to adverse events.

**Interpretation** In young people with recent-onset, clinical type 1 diabetes, 2·5 mg/kg and 0·5 mg/kg ATG reduced loss of β-cell function, showing the potential of an affordable, repurposed agent, ATG, in a low and safe dose, as a disease-modifying agent in this population.

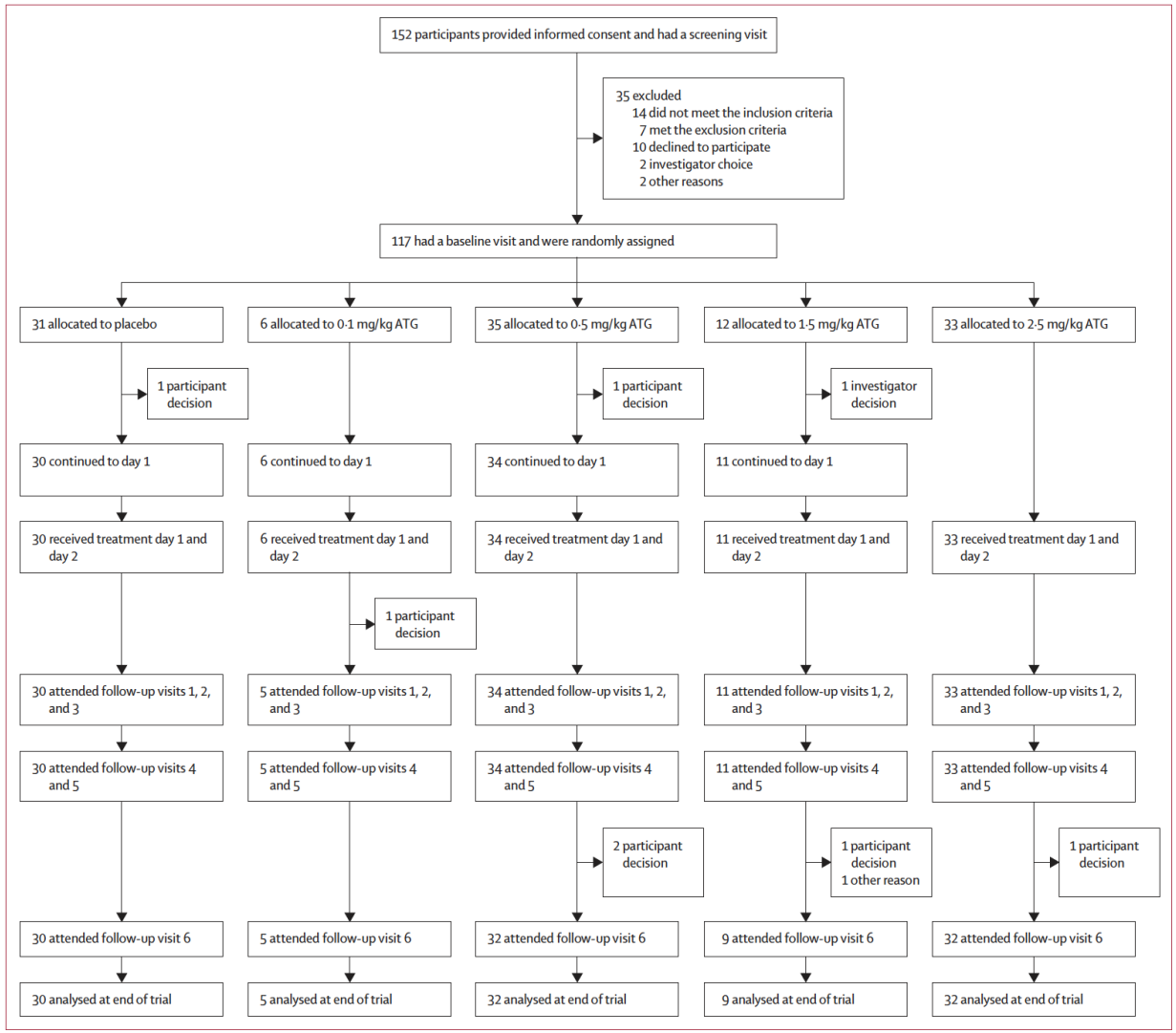



***Figure 1:*** **Trial profile**
ATG=antithymocyte globulin

| | Placebo group (n=31) | 0·1 mg/kg ATG group (n=6) | 0·5 mg/kg ATG group (n=35) | 1·5 mg/kg ATG group (n=12) | 2·5 mg/kg ATG group (n=33) |
|---|---|---|---|---|---|
| Age at randomisation, years | | | | | |
| 5–9 | 6 (19%) | 0 | 7 (20%) | 1 (8%) | 7 (21%) |
| 10–17 | 21 (68%) | 4 (67%) | 22 (63%) | 8 (67%) | 21 (64%) |
| 18–25 | 4 (13%) | 2 (33%) | 6 (17%) | 3 (25%) | 5 (15%) |
| Sex | | | | | |
| Male | 21 (68%) | 3 (50%) | 13 (37%) | 4 (33%) | 13 (39%) |
| Female | 10 (32%) | 3 (50%) | 22 (63%) | 8 (67%) | 20 (61%) |
| Ethnicity | | | | | |
| European | 28 (90%) | 6 (100%) | 31 (89%) | 10 (83%) | 31 (94%) |
| African | 1 (3%) | 0 | 1 (3%) | 1 (8%) | 1 (3%) |
| Asian | 0 | 0 | 2 (6%) | 1 (8%) | 1 (3%) |
| Mixed | 2 (6%) | 0 | 1 (3%) | 0 | 0 |
| BMI, kg/m² | 20·18 (3·68) | 23·30 (3·76) | 19·39 (3·25) | 19·83 (3·77) | 19·62 (3·46) |
| $HbA_{1c}$, % | 7·64 (1·10) | 7·20 (0·66) | 7·89 (1·32) | 7·97 (1·35) | 7·88 (1·17) |
| Insulin dose-adjusted $A_{1c}$ | 9·34 (1·78) | 8·32 (1·05) | 9·56 (2·02) | 9·45 (2·19) | 9·51 (1·67) |
| C-peptide AUC from 2-h MMTT, nmol/L per min* | 0·79 (0·62–0·97) | 1·06 (0·80–1·63) | 0·83 (0·67–1·15) | 0·86 (0·70–1·30) | 0·81 (0·68–0·95) |
| Time from type 1 diabetes diagnosis to randomisation, days | 54 (47–57) | 51 (43–58) | 50 (40–56) | 48 (34–57) | 51 (40–56) |
| Insulin delivery regimen | | | | | |
| Pump | 3 (10%) | 0 | 3 (9%) | 1 (8%) | 4 (12%) |
| Multiple dose | 28 (90%) | 6 (100%) | 32 (91%) | 11 (92%) | 29 (88%) |
| Number of positive autoantibodies at baseline | | | | | |
| 1 | 3 (10%) | 1 (17%) | 8 (23%) | 2 (17%) | 6 (18%) |
| 2 | 11 (35%) | 2 (33%) | 10 (29%) | 1 (8%) | 11 (33%) |
| 3 | 17 (55%) | 3 (50%) | 17 (49%) | 9 (75%) | 16 (48%) |

Data are n (%), mean (SD), or median (IQR). ATG=antithymocyte globulin. AUC=area under the curve. $HbA_{1c}$=glycated haemoglobin $A_{1c}$. MMTT=mixed-meal tolerance test.
*The mixed-meal-stimulated mean C-peptide concentration was calculated using the trapezoidal rule as the area under the concentration–time curve divided by 120 min.

***Table 1:*** **Baseline characteristics of the trial population by ATG dose**

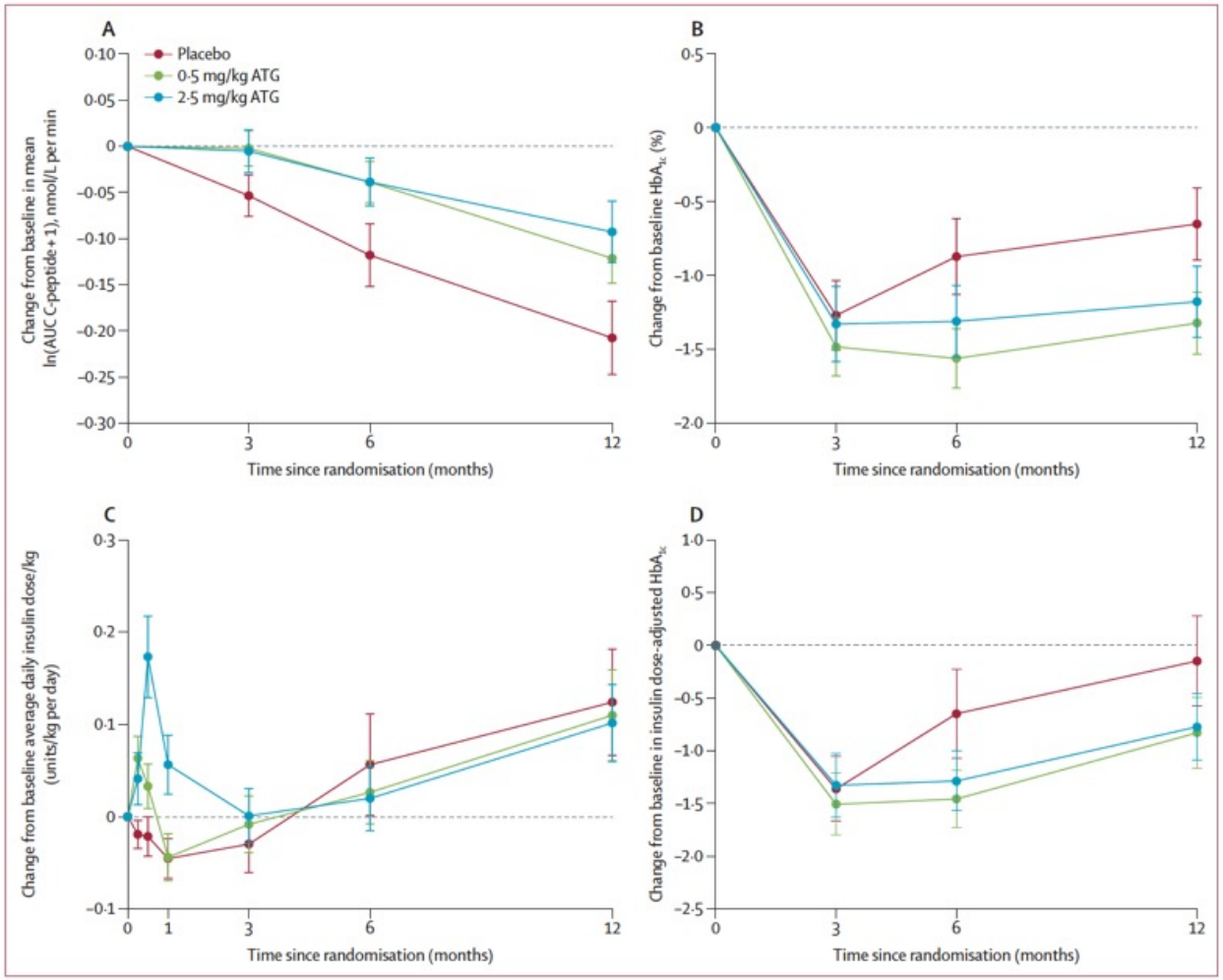



*Figure 2:* **Change from baseline over 12 months in efficacy outcomes**

(A) Change from baseline in ln(AUC C-peptide + 1). (B) Change from baseline in $HbA_{1c}$. (C) Change from baseline in daily insulin dose. (D) Change from baseline in insulin dose-adjusted $A_{1c}$. Data are shown for placebo (n=31), 0·5 mg/kg ATG (n=35), and 2·5 mg/kg ATG (n=33) groups. Data for 0·1 mg/kg ATG and 1·5 mg/kg ATG are shown in the appendix (pp 29–30, 32–37). Data are mean (SE). ATG=antithymocyte globulin. AUC=area under the curve. $HbA_{1c}$=glycated haemoglobin $A_{1c}$.

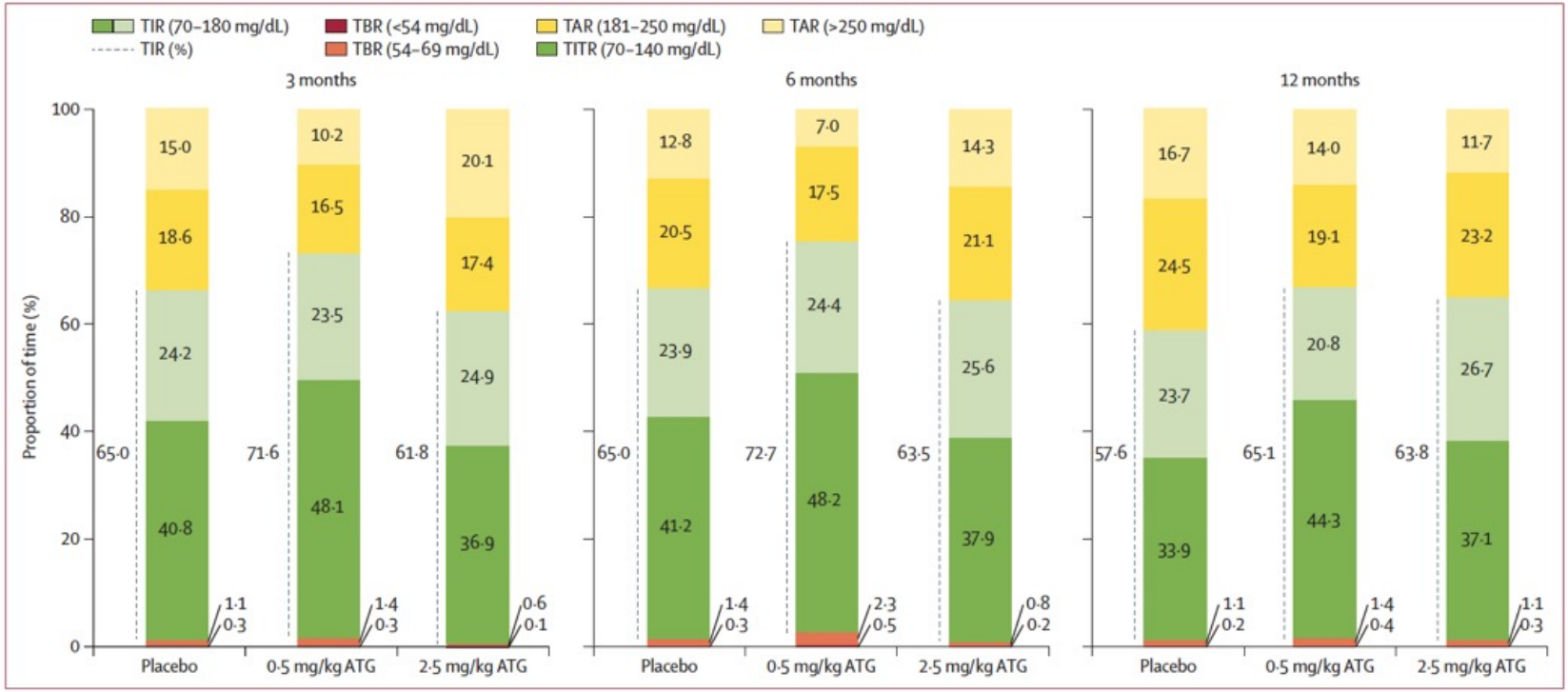



*Figure* 3: **Continuous glucose monitoring metrics**

ATG=antithymocyte globulin. TAR=time above range. TBR=time below range. TIR=time in range. TITR=time in tight range. Data are shown for placebo (n=31), 0·5 mg/kg ATG (n=35), and 2·5 mg/kg ATG (n=33) groups. Data for 0·1 mg/kg ATG and 1·5 mg/kg ATG are shown in the appendix (pp 10–11).

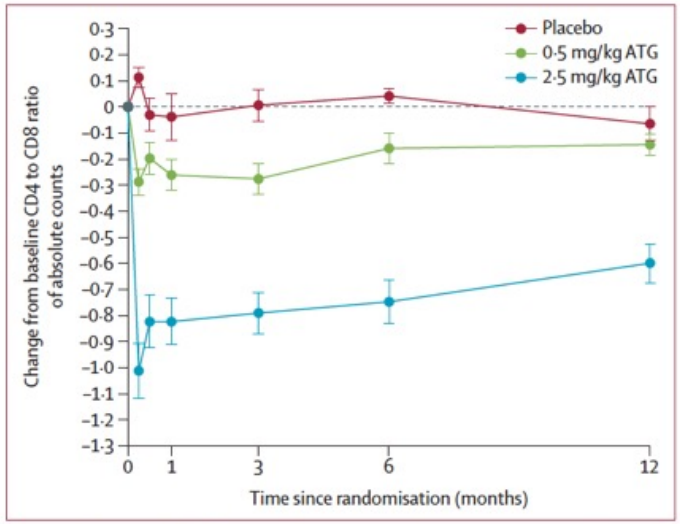



***Figure 4:*** **Change from baseline in the ratio of absolute counts of CD4 to CD8 T cells**

Data are shown for placebo (n=31), 0·5 mg/kg ATG (n=35), and 2·5 mg/kg ATG (n=33) groups at week 0 (baseline), week 1, week 2, month 1, month 3, month 6, and month 12. Data are mean (SE). ATG=antithymocyte globulin.

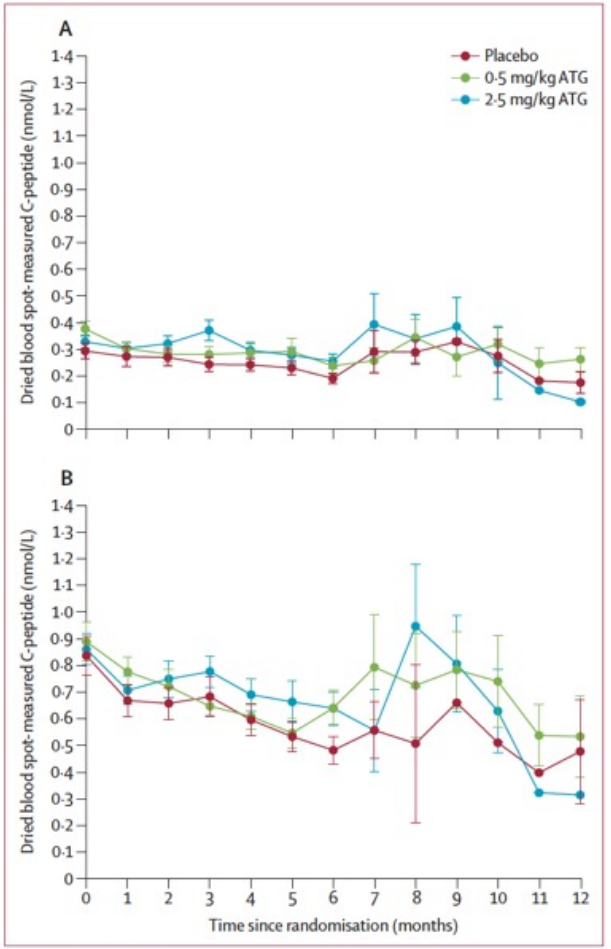



***Figure 5:*** **Dried blood spot-collected C-peptide concentrations**

(A) Home dried blood spot-collected C-peptide concentrations in the fasted state. (B) Home dried blood spot-collected C-peptide concentrations 60 min after a standard liquid meal test. Data are shown for placebo (n=31), 0·5 mg/kg ATG (n=35), and 2·5 mg/kg ATG (n=33) groups. Data are mean (SE). Note that after 6 months, data capture fell below 75% completeness.

| | Placebo group (n=30) | | 0·1 mg/kg ATG group (n=6) | | 0·5 mg/kg ATG group (n=34) | | 1·5 mg/kg ATG group (n=11) | | 2·5 mg/kg ATG group (n=33) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n (%) | Number of events or mean (SD) | n (%) | Number of events or mean (SD) | n (%) | Number of events or mean (SD) | n (%) | Number of events or mean (SD) | n (%) | Number of events or mean (SD) |
| Any adverse event | 30 (100%) | 272 | 6 (100%) | 58 | 34 (100%) | 334 | 11 (100%) | 99 | 33 (100%) | 422 |
| Any serious adverse event | 0 | 0 | 1 (17%) | 1 | 0 | 0 | 2 (18%) | 4 | 5 (15%) | 26 |
| Adverse events by severity | | | | | | | | | | |
| Grade 1 (mild) | 29 (97%) | 191 | 6 (100%) | 37 | 31 (91%) | 237 | 10 (91%) | 60 | 30 (91%) | 235 |
| Grade 2 (moderate) | 23 77%) | 80 | 5 (83%) | 21 | 28 (82%) | 92 | 9 (82%) | 33 | 31 (94%) | 180 |
| Grade 3 (severe) | 0 | 0 | 0 | 0 | 3 (9%) | 4 | 4 (36%) | 6 | 4 (12%) | 7 |
| Grade 4 (life-threatening) | 1 (3%) | 1 | 0 | 0 | 1 (3%) | 1 | 0 | 0 | 0 | 0 |
| Grade 5 (death related to adverse event) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Cytokine release syndrome | 0 | 0 | 2 (33%) | 2 | 8 (24%) | 9 | 2 (18%) | 3 | 11 (33%) | 16 |
| Occurred day 1 | 0 | 0 | 2 (33%) | 2 | 7 (21%) | 7 | 1 (9%) | 1 | 4 (12%) | 4 |
| Occurred day 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 (6%) | 2 |
| Occurred days 1 and 2 | 0 | 0 | 0 | 0 | 1 (3%) | 1 | 1 (9%) | 1 | 5 (15%) | 5 |
| Serum sickness | 0 | 0 | 0 | 0 | 11 (32%) | 11 | 6 (55%) | 6 | 27 (82%) | 27 |
| Time to onset, days* | .. | NA | .. | NA | .. | 9·5 (2·1) | .. | 12·0 (1·9) | .. | 10·6 (1·5) |
| Duration, days | .. | NA | .. | NA | .. | 2·9 (2·5) | .. | 6·3 (2·4) | .. | 5·5 (4·7) |
| Steroid treatment | 0 | .. | 0 | .. | 4 (12%) | .. | 0 | .. | 5 (15%) | .. |
| Lymphopenia | 6 (20%) | 6 | 2 (33%) | 2 | 12 (35%) | 14 | 5 (45%) | 6 | 14 (42%) | 17 |
| Anaemia | 4 (13%) | 4 | 0 | 0 | 1 (3%) | 1 | 0 | 0 | 4 (12%) | 4 |
| Thrombocytopenia | 0 | 0 | 0 | 0 | 0 | 0 | 1 (9%) | 1 | 3 (9%) | 3 |
| Abnormal liver enzymes† | 2 (7%) | 2 | 2 (33%) | 4 | 0 | 0 | 0 | 0 | 4 (12%) | 6 |
| Infections (including sepsis) | 9 (30%) | 12 | 2 (33%) | 3 | 9 (26%) | 14 | 3 (27%) | 4 | 13 (39%) | 16 |

Data are n (%), except where otherwise specified. ATG=antithymocyte globulin. NA=not applicable. *Time to onset from treatment day 1. †Aminotransferase increases or hyperbilirubinaemia.

*Table 2:* Adverse events across all visits

## Research in context

### Evidence before this study

The efficacy and safety of antithymocyte globulin (ATG) in preventing C-peptide loss as a marker of functional β-cell mass in people with recently diagnosed type 1 diabetes has been previously reported in three clinical studies. We searched PubMed for articles published in English between Jan 1, 2000, and Jan 1, 2025, using the terms ("anti-thymocyte globulin" AND "type 1 diabetes" AND "C-peptide") as well as ("ATG" AND "type 1 diabetes" AND "C-peptide"). The first study (the START trial) reported an absence of efficacy of 6·5 mg/kg ATG. In contrast, two subsequent studies showed the efficacy and safety of a lower dose, 2·5 mg/kg, of ATG, in adolescents and adults with new onset, clinical type 1 diabetes. A preliminary study by Haller and colleagues suggested less C-peptide loss in individuals treated with ATG and granulocyte-colony stimulating factor than with placebo. These observations were partially confirmed in a subsequent Trialnet study, in which C-peptide loss was lower in adolescents and adults treated with ATG, but not in those treated with ATG and G-CSF. More recently, Haller and colleagues reported 2-year clinical trial outcome data confirming a sustained effect of 2·5 mg/kg ATG on C-peptide and glycated haemoglobin $A_{1c}$ ($HbA_{1c}$). Mechanistic studies on the effects of ATG on lymphocyte subsets are emerging, but clarity is needed on dosing and whether the depletion of lymphocytes and the changes in CD4 to CD8 ratio observed with ATG are related to the metabolic treatment effect.

### Added value of this study

We investigated the efficacy and safety of different doses of ATG in young people (aged 5–25 years) with recently diagnosed, clinical type 1 diabetes using an innovative, adaptive trial design, allowing dropping (or restarting) doses on the basis of prespecified criteria. We not only achieved our primary endpoint, showing prevention of functional β-cell mass loss, measured as the difference in stimulated C-peptide at 12 months, for 2·5 mg/kg ATG versus placebo, but also identified a minimum effective dose of 0·5 mg/kg. Those treated with 0·5 mg/kg also had a lower $HbA_{1c}$ compared with placebo and had fewer side-effects compared with those treated with 2·5 mg/kg, in particular cytokine release syndrome and serum sickness. The novel, adaptive trial design of this study with progressive age drop-down and its execution in the context of a clinical trial platform with accredited clinical trial sites (INNODIA), allowed us to test multiple doses of ATG over a large age range, illustrating that this novel way of testing disease-modifying therapies could allow an increased pace of finding treatments to arrest type 1 diabetes progression.

### Implications of all the available evidence

Our findings strengthen the potential of ATG as a safe agent for therapy in children and adolescents with recent-onset, stage 3 type 1 diabetes. Our study also emphasises the feasibility of adaptive trial designs for disease-modifying therapies in type 1 diabetes. The observations that a therapy such as ATG is most effective in the youngest participants suggest there should be an alteration in the regulatory pathways for testing and approving disease-modifying therapies in type 1 diabetes.

## *The Lancet* Series on Alzheimer's Disease 1

# New landscape of the diagnosis of Alzheimer's disease

Alzheimer's disease involves a drastic departure from the cognitive, functional, and behavioural trajectory of normal ageing, and is both a dreaded and highly prevalent cause of disability to individuals, and a leading source of health and social care expenditure for society. Before the advent of biomarkers, post-mortem examination was the only method available to establish a definitive diagnosis. In this first paper of the Series, we review state-of-the-art diagnostic practices and the typical patient journey in specialist settings, where clinicians engage in a differential diagnosis to establish whether Alzheimer's pathology (cerebral deposition of β-amyloid and hyperphosphorylated tau) is a contributor to cognitive impairment. Biomarkers indicating dysregulation of β-amyloid and tau homeostasis, measured with PET and cerebrospinal fluid analysis, allow a molecular-level diagnosis—a mandatory step in defining eligibility for the recently approved anti-amyloid treatments. We anticipate that easily accessible blood biomarkers, already available in some countries, will lead to a new diagnostic revolution and bring about major changes in health-care systems worldwide.

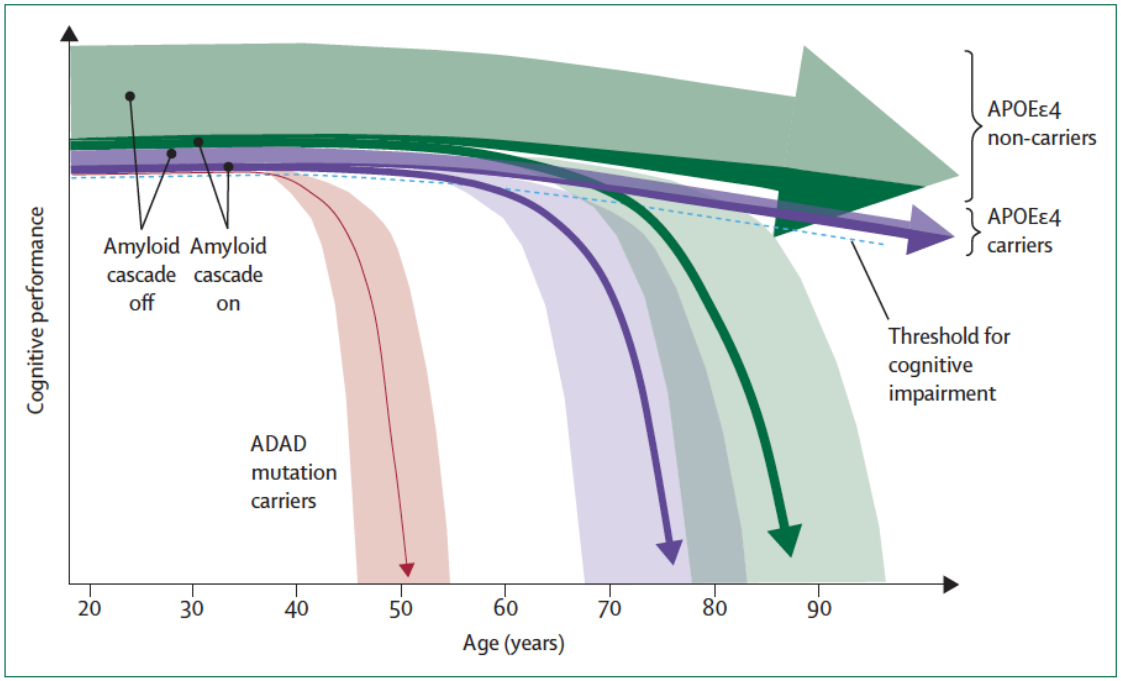



***Figure 1:*** **Cognitive trajectories during ageing by genetic and biomarker status**
Trajectories are those implied by the pathophysiological probabilistic amyloid cascade model of Alzheimer's disease[58] and are consistent with current diagnostic frameworks for Alzheimer's disease.[39,40] Arrows denote cognitive trajectories of autosomal dominant Alzheimer's disease mutation carriers (red), *APOE* ε4 allele carriers (purple), and non-carriers (green). Dark and light colours denote those who enter (on amyloid cascade) and do not enter the amyloid cascade (off). Arrow thickness is roughly proportional to the population prevalence. Red, purple, and green shading around some arrows denote variability within trajectories due to stochastic factors (non-*APOE* genes, non-Alzheimer's disease pathologies, lifestyle factors, frailty, and environmental exposures such as literacy, educational attainment, and early life cognitive engagement). More details in appendix (p 2).

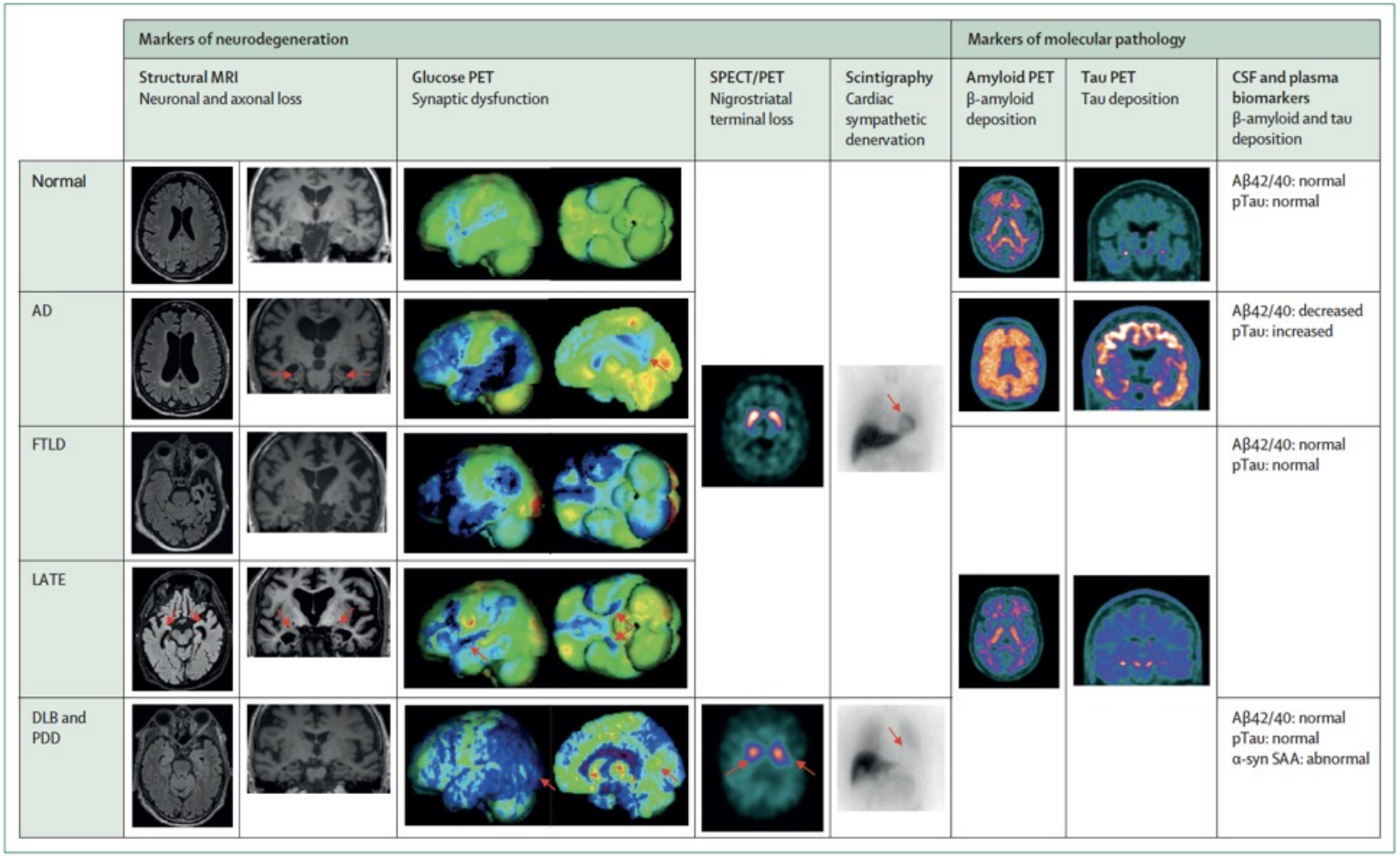



*Figure 4*: **Typical biomarker profiles across pure pathology neurodegenerative cognitive disorders.**
Blue colour in glucose PET renderings denotes substantial hypometabolism. Orange/red/purple/white colours in nigrostriatal SPECT imaging and amyloid and tau PET denote increased tracer uptake. Images come from the archive of one of the co-authors (VG). More details in appendix (p 8). AD=Alzheimer's disease with typical amnestic phenotype. CSF=cerebrospinal fluid. DLB=dementia with Lewy bodies. FTLD=frontotemporal lobar degeneration with behavioural phenotype. LATE=limbic-predominant age-related TDP-43 encephalopathy.[110] PDD=Parkinson's disease dementia. SAA=seed amplification assay. SPECT=single-photon emission computed tomography.

## Conclusions

In this Series paper, we have shown that the theory and practice surrounding Alzheimer's disease and its diagnosis are undergoing dynamic and lively evolution. A better understanding of the natural history of biomarkers associated with Alzheimer's disease pathology has enabled the development of patho-physiologically sensible and clinically useful diagnostic criteria. The increased use of, and experience with, biomarkers in clinical settings has facilitated the development of diagnostic workflows that support earlier, more accurate, and sustainable diagnosis and differential diagnosis of Alzheimer's disease. Advances in the biomarker field have improved the accuracy and structure of diagnostic assessment in all patients, regardless of whether molecular biomarkers are used.

The availability of anti-amyloid monoclonal antibodies in some countries has further accelerated the uptake of diagnostic biomarkers, although the benefits of a timely and accurate diagnostic assessment extend well beyond the indications for monoclonal antibody treatment. Exciting technological advancements have enabled the development of easily accessible blood-based biomarkers, which have already started yet another diagnostic revolution, with radical changes in the diagnostic patient journey in high-income and hopefully soon in low-income and middle-income countries. The state-of-the-art treatments of cognitive and non-cognitive behavioural symptoms in patients with Alzheimer's disease will be addressed in the second paper of this Series on Alzheimer's disease.[14]

*The Lancet* Series on Alzheimer's Disease 2

# Treatment for Alzheimer's disease

Over the last three decades, the evidence on how to best treat the cognitive and non-cognitive symptoms of patients with Alzheimer's disease has increased. Although these pharmacological and non-pharmacological strategies have significantly improved health outcomes for patients with Alzheimer's disease, many lack stringent evidence of efficacy. In this second paper of the Series, we provide practical and realistic advice on how to prioritise pharmacological and non-pharmacological strategies to ameliorate cognitive impairment and behavioural and psychological symptoms of dementia. In this clinical environment, dementia specialists are faced with the challenge of holistically integrating the much anticipated and, in some respects, controversial anti-β amyloid monoclonal antibodies. Here, we present the current approval scenario of monoclonal antibodies, our view on how they might further contribute to improve patients' quality of life, and how they could be seamlessly integrated with existing best care options.

**Panel 1: Practical advice for a judicious use of psychotropic drugs in patients with behavioural and psychological symptoms of dementia**

**Be aware of the neurochemical properties of prescribed drugs**

Most psychotropics target multiple neurochemical systems. At therapeutic doses, the dominant receptor activity drives benefits and adverse effects. For instance, risperidone's strong dopamine blockade causes both its high antipsychotic activity and the high risk of parkinsonism. Quetiapine's milder dopaminergic and stronger antihistaminic effects lead to lower antipsychotic activity and risk of parkinsonism, but more sedation compared with risperidone. Other drugs with antihistaminergic and anticholinergic effects can result in sedation and worsened cognition.[36,56]

**Avoid drugs with anticholinergic activity**

Tricyclic antidepressants, paroxetine, and olanzapine have high propensity to cause confusion, dry mouth, blurred vision, urinary retention, constipation, and increased intraocular pressure, and should be strictly avoided in older people (>65 years) with cognitive impairment.

**Minimise number of psychotropic drugs**

Behavioural and psychological symptoms of dementia (BPSD) often occur in clusters; for example, depression and insomnia, agitation and insomnia, or anxiety and depression. Whenever possible, use one drug with dual efficacy rather than two drugs. For instance, in a patient with daytime agitation and insomnia, use trazodone during the day and (at higher dose than in the day) at bedtime, rather than risperidone during the day and a hypnotic or a benzodiazepine at bedtime.

**Start low, go slow, prescribe, and revise**

Start at one-eighth to one-quarter of the adult dose and titrate gradually over 2–4 weeks. Short-loop follow-up assessments of efficacy and tolerability after every drug increment is ideal. As BPSD are inherently intermittent, treatments should never be carried over indefinitely. A follow-up plan should be decided at the start of treatment, and tapering-off attempts should be carried out after 3 months of stable behaviour.

**Switch with a scheme**

If a drug is not, or insufficiently, effective after an adequate therapeutic trial (usually ≥6 weeks), discontinuation and switching to an alternative is indicated rather than adding on. Different switch schemes can be considered depending on drugs and BPSD: abrupt switch, taper switch, cross-taper switch, or plateau cross-taper switch.[57]

**Panel 2: Case examples: treatment of behavioural and psychological symptoms of dementia with integrated non-pharmacological and pharmacological interventions**

Person A is a woman, aged 86 years, who has Alzheimer's disease of moderate cognitive and functional severity and who lives in a nursing home. She becomes irritable and verbally aggressive when being helped out of bed in the morning, to move to the dining room for meals, and to go to bed, which has led to frustration among staff. She is prescribed analgesics for arthritis, which she never requests. The irritability and verbal aggression are situational, possibly triggered by pain and exacerbated by interactions with staff. After exclusion of other active medical conditions, regular analgesia is prescribed[37] and staff are trained to develop a non-threatening communication pattern, using soft tones and calming, non-verbal behaviour, and to take more time during interactions. Agitation and aggression resolved within 2 weeks. Person A is regularly monitored for the re-emergence of the symptoms.

Person B is a woman, aged 82 years, who has Alzheimer's disease of moderate cognitive and functional severity and who lives in the community with her daughter. For the past few weeks, when she is alone in the afternoons, about every other day, she starts to become worried that her handbag has been stolen and then shouts to her daughter for help to find the thieves. She usually calms down over about 15 min with a reassuring conversation. After the exclusion of active medical conditions and an ECG to check the QT corrected for heart rate interval, she is prescribed citalopram. Her daughter receives positive reinforcement about the value of what she is already doing. The daughter is also helped to arrange for a friend to visit person B regularly while she is on her own. The frequency of episodes of agitation is significantly reduced after 4 weeks.

Person C is a man, aged 62 years, who has early onset Alzheimer's disease of moderate global severity and who lives in a nursing home. He has been constantly irritable and has hit members of staff and other residents on multiple occasions, despite the staff's kind and understanding behaviour. He has also been tearful and has had low in mood at times, but he is eating and sleeping well. Although irritability happens during interactions, the triggers are not specific. After exclusion of active medical conditions and an ECG to check QT corrected for heart rate, citalopram is prescribed for 4 weeks, but without appreciable effectiveness. Following a risk–benefit assessment, person C is switched to risperidone over 4 weeks with a cross-taper switch scheme. Brexpiprazole would have been equally indicated. Doses of risperidone or brexpiprazole should be started low and increased over 2–4 weeks to identify the lowest effective dose, with careful monitoring for oversedation, reduced mobility, or other adverse effects. As it usually takes at least 4 weeks for the benefits of slow-tapering antipsychotic medication to become evident, it is also important to help to reduce potential triggers—eg, by enabling person C to spend more time in a quiet lounge or his room (with regular interaction). Helping him feel more at home in the nursing home, with more regular personalised interaction with a key member of care staff and increasing the number of personal possessions in his room, might also help. Regular follow-up of treatment is paramount.

| | Symptomatic drugs | β-amyloid immunotherapies |
|---|---|---|
| Molecules | Cholinesterase inhibitors (donepezil, galantamine, or rivastigmine) and memantine | Anti-β amyloid monoclonal antibodies (donanemab or lecanemab) |
| Mechanism of action | Receptor agonist or antagonist | Microglia-mediated removal of aggregated β-amyloid |
| Administration route and frequency | Oral (once or twice a day) or transdermal (once a day, twice per week, or weekly) | Donanemab intravenously every 4 weeks; lecanemab intravenously every 2 weeks; and subcutaneous formulations under development |
| Indication | Clinical diagnosis of Alzheimer's disease with mild to moderate (cholinesterase inhibitors) and moderate to severe (memantine) cognitive impairment; biomarkers not mandatory | Diagnosis of early Alzheimer's disease evidenced by amyloid biomarkers, cognitive impairment of at least mild severity, and no or only mild functional impairment |
| Efficacy | Cognitive benefit while on therapy equivalent to ~6 months of decline; improved cognitive function can be appreciated within 12 weeks from treatment inception | 27–35% less compared with untreated decline in global cognitive or functional endpoints at 18 months from treatment inception; longer term outcomes currently unknown; and no improvement of cognitive function to be expected |
| Tolerability | Good with appropriate titration (occasional side-effects of nausea, vomiting, diarrhoea, dizziness, headache, or bradycardia) | *APOE*-dependent local brain oedema and bleeding (ARIA); infusion-related reactions; and better tolerability with slow titration |
| Monitoring of efficacy | Clinical assessment, cognitive tests, and functional scales | Clinical assessment, cognitive tests, and functional scales |
| Monitoring of adverse events | Clinical follow-up every 6–12 months | Typically, three brain MRI scans in the initial 12 months of treatment and clinical monitoring for symptoms attributable to ARIA, which determines if treatment needs to be paused or discontinued, and prompts additional MRI until ARIA resolution |
| Discontinuation | When reaching severe or very severe cognitive or functional impairment; intolerance or adverse events; or difficulties in administration of the drug (eg, dysphagia) | Donanemab when amyloid negative on amyloid PET; lecanemab unknown, trials ongoing |

ARIA=amyloid-related imaging abnormalities.

***Table 1:*** **Features of symptomatic therapies and β-amyloid immunotherapies**

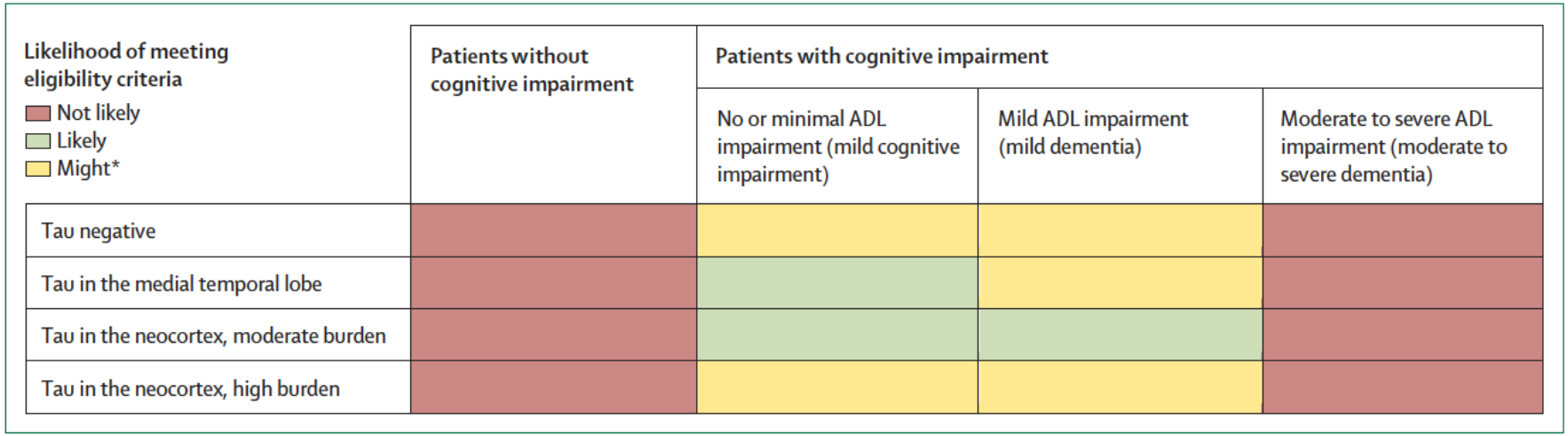



***Figure 1:*** **Current clinical eligibility for anti-β amyloid monoclonal antibody treatment for patients at memory clinics with positive biomarkers for brain beta amyloidosis**

Patients without cognitive impairment includes patients with or without cognitive complaints (subjective cognitive decline). This representation was adapted from Jack and colleagues[109] and simplified for patients at memory clinics. Terms are defined in the appendix (pp 7–9). ADL=activities of daily living. *Patients have a greater likelihood of meeting exclusion criteria, or the risk or burden of treatment might outweigh potential benefit.

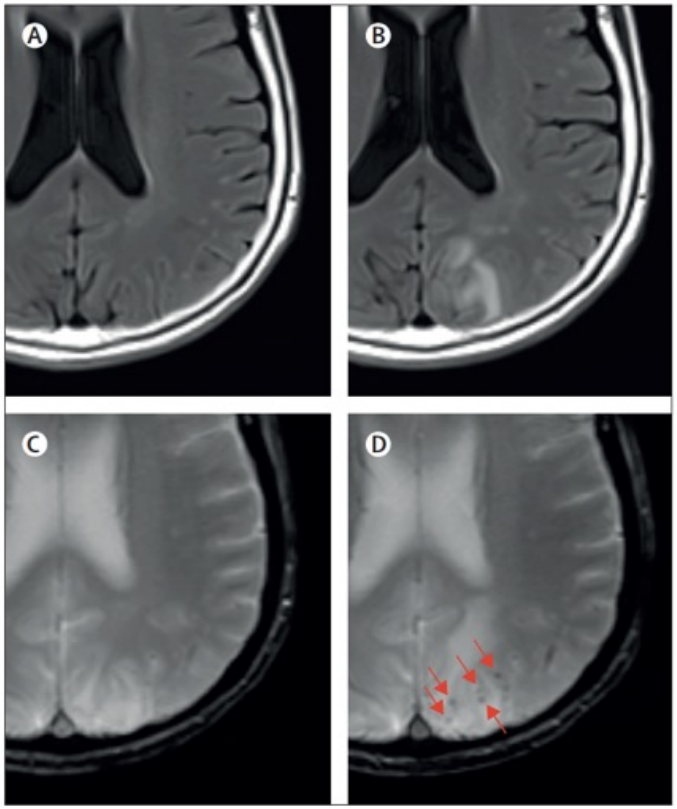



*Figure 2:* **ARIA-E and ARIA-H**
(A) Baseline brain MRI of a patient treated with an anti-β amyloid monoclonal antibody. Radiologically mild left parietal ARIA on fluid-attenuated inversion recovery (B) and T2*-weighted MRI (C). The patient was asymptomatic and the ARIA was detected during a routine follow-up scan. Immunotherapy was continued according to recommendations.[105] (D) After 1 month, microbleeds (ARIA-H) were detected on T2*-weighted MRI in the region of ARIA-E. ARIA=amyloid-related imaging abnormalities. ARIA-E=amyloid-related imaging abnormalities with oedema. ARIA-H=amyloid-related imaging abnormalities with microhaemorrhages.

| | Very mild impairment | Mild impairment |
|---|---|---|
| Memory | Consistent slight forgetfulness; partial recollection of events; or benign forgetfulness | Moderate memory loss; more marked for recent events; or interferes with everyday activities |
| Orientation | Fully oriented except for slight difficulty with time relationships | Moderate difficulty with time relationships; oriented for place at examination; or might have geographical disorientation |
| Judgement and problem solving | Slight impairment in everyday problems (business and financial affairs); or slight impairment in judgement of past performance | Moderate difficulty in handling problems, similarities, and differences; or social judgement usually maintained |
| Community affairs | Slight impairment; or still able to work and drive | Unable to function independently; might engage in some activities; appears normal to casual inspection; or can no longer work, but can walk around local area |
| Home-life and hobbies | Life at home; or home-life, hobbies, and intellectual interests slightly impaired | Mild, but definite, impairment of function at home; more difficult chores and interests abandoned; or more complicated hobbies and interests abandoned |
| Personal care | Fully capable of self-care | Needs prompting |

Very mild impairment refers to a score of 0·5 on CDR-SB scale, whereas mild impairment refers to a score of 1. The effects of donanemab and lecanemab consist of around 0·5 points less progression on the CDR-SB scale over 18 months. We illustrate how this amount of benefit might translate in a patient's daily life when, for example, transitioning from very mild to mild impairment in one of the scale domains. The benefit of about 0·5 points on the CDR-SB scale shown in the phase 3 clinical trials of lecanemab and donanemab is the sum of changes across all six CDR domains (memory, orientation, judgment and problem solving, community affairs, home-life and hobbies, and personal care).[101,102] Scores 0, 2, and 3 (no, moderate, and severe impairment, respectively) are not shown as they are not pertinent to patients eligible for treatment with these drugs. Modified from Morris.[115] CDR=Clinical Dementia Rating. CDR-SB=Clinical Dementia Rating-Sum of Boxes.

*Table 2:* **Clinical meaningfulness of treatment with donanemab and lecanemab on the CDR-SB scale**

| | Lecanemab (n=898) | Donanemab (n=853) | All placebo (n=1771) |
|---|---|---|---|
| **Proportion relative to treated or placebo** | | | |
| Of any severity | | | |
| All | 12·6% (10·6–14·9); 9 (8–12) | 24·0% (21·3–27·0); 5 (4–5) | 1·8% (1·3–2·5) |
| ε4 non-carrier | 5·4% (3·3–8·7); 20 (13–43) | 15·7% (11·7–20·7); 7 (5–10) | 0·6% (0·2–1·6) |
| ε4 heterozygous | 10·9% (8·4–14·0); 11 (8–17) | 22·8% (19·2–26·9); 5 (4–6) | 1·9% (1·2–3·0) |
| ε4 homozygous | 32·6% (25·4–40·7); 3 (3–5) | 40·6% (32·9–48·8); 3 (2–4) | 3·6% (2·0–6·5) |
| Symptomatic | | | |
| All | 2·8% (1·9–4·1); 36 (26–59) | 5·8% (4·5–7·4); 18 (14–24) | 0·1% (0–0·3) |
| ε4 non-carrier | 1·4% (0·6–3·6); 70 (35–2565) | 4·1% (2·4–7·1); 24 (16–54) | 0% (0–0·7) |
| ε4 heterozygous | 1·7% (0·8–3·3); 60 (36–191) | 6·1% (4·4–8·5); 16 (12–25) | 0% (0–0·4) |
| ε4 homozygous | 9·2% (5·5–15·1); 11 (7–23) | 7·7% (4·6–12·8); 14 (9–34) | 0·3% (0·1–1·8) |
| Severe on MRI | | | |
| All | 1·0% (0·5–1·9); 100 (60–285) | 1·6% (1–2·7); 61 (40–126) | 0% (0–0·2) |
| ε4 non-carrier | 0% (0–1·4); infinity | 0·4% (0·1–2·2); 255 | 0% (0–0·7) |
| ε4 heterozygous | 0·4% (0·1–1·5); 240 | 2·0% (1·1–3·7); 50 (31–142) | 0% (0–0·4) |
| ε4 homozygous | 5·0% (2·4–9·9); 20 (12–73) | 2·8% (1·1–7·0); 36 (18–1057) | 0% (0–1·4) |
| Clinically serious | | | |
| All | 0·3% (0·1–1·0); 299 | 1·5% (0·9–2·6); 65 (43–142) | 0% (0–0·2) |
| ε4 non-carrier | 0% (0–1·4); infinity | 0·4% (0·1–2·2); 255 | 0% (0–0·7) |
| ε4 heterozygous | 0·4% (0·1–1·5); 240 | 1·8% (0·9–3·5); 57 (34–180) | 0% (0–0·4) |
| ε4 homozygous | 0·7% (0·1–3·9); 141 | 2·8% (1·1–7·0); 36 (18–1057) | 0% (0–1·4) |

(Table 3 continues on next page)

(Continued from previous page)

| | Lecanemab (n=898) | Donanemab (n=853) | All placebo (n=1771) |
|---|---|---|---|
| **Proportion relative to radiological ARIA-E** | | | |
| Symptomatic | | | |
| All | 22·1% (15·5–30·6); NA | 23·8% (18·8–29·5); NA | 2·9% (0·5–14·9) |
| ε4 non-carrier | 26·7% (10·9–52); NA | 27·9% (16·7–42·7); NA | 0% (0–56·1) |
| ε4 heterozygous | 15·4% (8–27·5); NA | 25·4% (18·6–33·6); NA | 0% (0–16·8) |
| ε4 homozygous | 28·3% (17·3–42·5); NA | 18·6% (11·2–29·2); NA | 9·1% (1·6–37·7) |
| Severe on MRI | | | |
| All | 8·0% (4·2–14·4); NA | 6·8% (4·1–11·1); NA | 0% (0–10·7) |
| ε4 non-carrier | 0% (0–20·4); NA | 2·5% (0·4–12·9); NA | 0% (0–56·1) |
| ε4 heterozygous | 3·8% (1·1–13); NA | 8·7% (4·7–15·8); NA | 0% (0–17·6) |
| ε4 homozygous | 15·2% (7·6–28·2); NA | 6·9% (2·7–16·4); NA | 0% (0–27·8) |
| Clinically serious | | | |
| All | 2·7% (0·9–7·5); NA | 6·3% (3·7–10·5); NA | 0% (0–10·7) |
| ε4 non-carrier | 0% (0–20·4); NA | 2·5% (0·4–12·9); NA | 0% (0–56·1) |
| ε4 heterozygous | 3·8% (1·1–13); NA | 7·8% (4–14·6); NA | 0% (0–17·6) |
| ε4 homozygous | 2·2% (0·4–11·3); NA | 6·9% (2·7–16·4); NA | 0% (0–27·8) |

Data are % (95% CI); number needed to harm (95% CI). Number needed to harm data are number of people who are expected to be treated for one adverse event to occur. The method for calculating number needed to harm is provided in the appendix (p 5). As the inclusion criteria for the trials were largely similar, placebo groups are merged. Data on the incidence of symptomatic ARIA by *APOE* ε4 genotypes were not available in the donanemab placebo-controlled phase 3 trial.[101] Rates have been computed based on pooled phase 2 and phase 3 placebo-controlled trials.[120] ARIA-E=amyloid-related imaging abnormalities with oedema. NA=not applicable.

***Table 3:*** **Incidence of ARIA-E in randomised controlled trials of lecanemab and donanemab and number needed to harm**

## Conclusions

Knowledge and practice around therapeutical strategies to improve the quality of life of people with Alzheimer's disease have increased dramatically over recent decades. Structured non-pharmacological programmes are being used for the management of BPSDs along with better tolerated drugs than those used previously. Symptomatic drugs for cognitive impairment, although with limited efficacy, have forced health-care systems to organise dedicated expert care networks, thus facilitating access to diagnosis and care. Anti-β amyloid monoclonal antibody treatment for Alzheimer's disease represents the latest tool and promise long-term improvements of patients' quality of life.

Every step of this ever-improving journey has come at a cost for society, and anti-β amyloid monoclonal antibodies will not be an exception. The debate on the clinical meaningfulness of the effect of anti-β amyloid monoclonal antibodies, their cost–benefit ratio, the appropriateness of resource allocation, and the benefit to the quality of life of society at large will engage the community of Alzheimer's disease experts and decision makers for years to come. Data from real life observational cohorts from high-income countries and from low-income and middle-income countries will be key for informed choices. However, the amount of resources to devote to ameliorate the quality of life of people with Alzheimer's disease will ultimately be a political and societal—not a clinical—decision. Insight into some elements of this debate is provided in the third paper of this Series on controversies and the future.[110]

*The Lancet* Series on Alzheimer's Disease 3

# Alzheimer's disease outlook: controversies and future directions

For the first time, reductions in cerebral β-amyloid pathology load and rate of cognitive and functional decline have been achieved in Alzheimer's disease, through pharmacological intervention in randomised controlled trials. However, the results from phase 3 randomised controlled trials of anti-β amyloid monoclonal antibodies are interpreted in different ways, with some experts supporting a clinically meaningful disease-modifying effect, and others judging insufficient benefit-to-risk ratio and opposing market authorisation. In the final paper of this Series, we discuss these contrasting views, all of which wish to contribute to improvements in the quality of life of people with, or at risk of, Alzheimer's disease. We contrast the efficacy, societal costs, and generalisability of monoclonal antibodies for Alzheimer's disease to biologics for other conditions (eg, cancer, multiple sclerosis, and rheumatoid arthritis) and set this debate in the larger context of modern personalised medicine. We discuss current practice implications, future developments directed to β-amyloid and non-amyloid targets that might have more clinical efficacy and less adverse effects for those with the disease, and large-scale prevention interventions for those at risk.

| | Disease centred | Patient centred | Population centred |
|---|---|---|---|
| **Specificities** | | | |
| Core goal | To identify and accurately measure in vivo mechanisms that cause cognitive impairment | To address patients' needs | To improve the health of the whole population |
| Scientific discourse | Understanding disease biology will enable development of disease-specific biomarkers and disease-modifying treatments; disease-modifying treatments for individuals will contribute to improvement of population health | Any intervention to improve the quality of life of patients is acceptable, regardless of the depth of understanding of their biological effect | Dementia is a multifactorial syndrome most commonly affecting people who are older than 80 years; a significant impact on population health can be achieved through interventions relevant to large strata of the population with, or at risk of, dementia |
| Knowledge source | Observational cohorts with in vivo deep phenotyping (clinical, biomarkers, genetics, and pathology) that span the continuum of Alzheimer's disease, from preclinical to cognitively impaired stages | In specialised care knowledge comes mainly from the disease-centred literature; in general practice knowledge comes mainly from the population-centred literature | Population-representative cohorts |
| Definition of Alzheimer's disease | Alzheimer disease is a biological construct; the disease is defined by its unique neuropathology; the disease begins before the onset of symptoms; the disease is assumed to cause symptoms | Alzheimer's disease is a clinical-biological construct; the disease starts with the first symptoms; diagnostic labels should reflect shared physician's and patient's narratives | Alzheimer's disease pathology is frequent in people without dementia, and most people with dementia have mixed pathologies; Alzheimer's disease as a distinct, homogeneous disease entity is rare in the general population |
| Diagnosis of Alzheimer's disease | Via biomarkers of Alzheimer's disease pathology | Via clinical assessment and biomarkers of Alzheimer's disease pathology | Via clinical assessment; biomarker assessment in subgroups of the general population to assess risk |
| Interventions for Alzheimer's disease | Drugs against Alzheimer's disease pathology and symptomatic drugs | Symptomatic drugs, drugs against Alzheimer's disease pathology, and psychosocial interventions | Interventions on social determinants and prevention of modifiable risk factors |
| Efficacy of anti-β amyloid monoclonal antibodies | Monoclonal antibodies remove plaque, but do not eliminate the Alzheimer's disease pathophysiological process; the earlier they are taken, the more effective they are | Monoclonal antibodies are a partially effective but relevant, therapeutic strategy contributing to delay of the progression of cognitive deficits and disability | Monoclonal antibodies have a small clinical effect in few selected patients at enormous social costs that will deflect resources from those at greater need |
| **Commonalities** | | | |
| Aim of clinical research on Alzheimer's disease and other cognitive disorders | Improving the cognitive health and quality of life of individuals and the community | As for previous column | As for previous column |
| Role of co-pathology | Alzheimer's disease pathology incompletely explains cognitive impairment in many individuals who are older (>85 years). Alzheimer's disease pathology is common in those who do not develop cognitive impairment and co-pathology is increasingly prevalent with older age (vascular lesions, α-synuclein, or TDP-43, among others); although significant levels of neocortical tau pathology are associated with progression to cognitive impairment, a proportion of individuals with Alzheimer's disease pathology never develop cognitive impairment within their lifetimes; increasing co-pathology increases likelihood of cognitive impairment | As for previous column | As for previous column |
| Role of brain reserve | Genetic, brain vascular, environmental, and social factors can significantly modulate the phenotypic expression of Alzheimer's disease pathology | As for previous column | As for previous column |
| Biomarker use | At present, biomarkers should not be used in people without cognitive impairment outside the context of observational or therapeutic research studies because no treatments have yet been approved for this population | As for previous column | As for previous column |
| Indication for anti-β amyloid monoclonal antibodies | People with Alzheimer's disease at the mild cognitive impairment or mild dementia stage | As for previous column | In tax-funded health systems, these drugs are unlikely to be considered cost-effective and, therefore, should not be rolled out |
| Contraindication for anti-β amyloid monoclonal antibodies | Patients at moderate or severe stages, with medical contraindications, or with comorbid brain pathology where Alzheimer's disease seems clinically unlikely to be the major cause of impairment; these patients should receive mainly supportive and psychosocial care | As for previous column | As for previous column |

(Table 1 continues on next page)

(Continued from previous page)

| | Disease centred | Patient centred | Population centred |
|---|---|---|---|
| People with cognitive impairment and positive Alzheimer's disease biomarkers | Drugs directed against Alzheimer's disease pathology including anti-β amyloid monoclonal antibodies could, when shown to be effective, be used to reduce the risk of incident cognitive impairment and dementia; the indication will depend on an overall assessment of co-occurring risk factors and absolute risk | As for previous column | The drugs would need to be part of a screening programme for which the evidence clearly meets the established WHO criteria,[33] including net population benefit and cost-effectiveness |
| Health-care delivery model | Interventions for individuals and the community should be developed in synergy to improve general health and quality of life | As for previous column | As for previous column |

The caricatured profiles are intended to clearly differentiate between different perspectives on addressing the Alzheimer's disease conundrum.[32] Disease-centred,[32] patient-centred,[34] and population-centred[35] approaches aim to help the field answer complex questions and nuanced, and heterogeneous views exist within and across these perspectives. Views on appropriate use of biomarkers and drugs are based on current knowledge and should be updated as new evidence accumulates. More information on anti-β amyloid monoclonal antibodies can be found in the second paper of this Series.[3] Alzheimer's disease pathology includes brain deposition of β-amyloid plaques and tau neurofibrillary tangles.

***Table 1:*** **Paradigmatic approaches to solving the Alzheimer's disease conundrum**

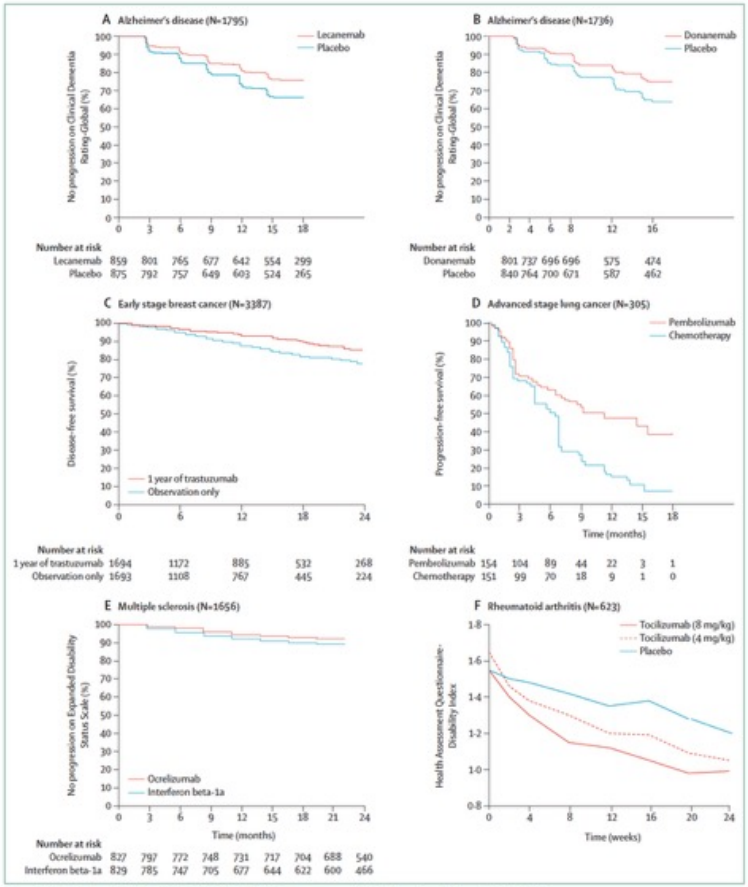



*Figure 1:* **Effect of monoclonal antibodies in Alzheimer's disease, cancer, multiple sclerosis, and rheumatoid arthritis**
All panels show time-to-event data except for tocilizumab, where mean scale values are shown. Group sizes at the start of the observation period are shown at the bottom of each graph except for tocilizumab. Curves are taken from the original publications and redrawn for consistency of the y-axis scale except for tocilizumab due to copyright regulations. (A) Reproduced from van Dyck and colleagues,[57] with permission from the Massachusetts Medical Society. (B) Reproduced from Sims and colleagues[58] with permission from American Medical Association. (C) Reproduced from Piccart-Gebhart and colleagues[60] with permission from Massachusetts Medical Society. (D) Reproduced from Reck and colleagues,[61] with permission from the Massachusetts Medical Society. (E) Reproduced from Hauser and colleagues,[62] with permission from the Massachusetts Medical Society. (F) 566 of 623 participants completed the study. Reproduced from Smolen and colleagues.[63] The Clinical Dementia Rating-Global is a 0-to-3 scale version of the Clinical Dementia Rating scale, where levels are 0, 0·5, 1, 2, and 3, and extreme values have similar meaning to the Clinical Dementia Rating-Sum of Boxes. More details on the Clinical Dementia Rating-Sum of Boxes, progression-free survival, disease-free survival, Expanded Disability Status Scale, and Health Assessment Questionnaire-Disability Index can be found in the appendix (p 2).

| | Alzheimer's disease | Alzheimer's disease | Early stage breast cancer | Lung cancer | Multiple sclerosis | Rheumatoid arthritis |
|---|---|---|---|---|---|---|
| **Drug features** | | | | | | |
| Drug | Lecanemab[57] | Donanemab[58] | Trastuzumab[60] | Pembrolizumab[61] | Ocrelizumab[62] | Tocilizumab[63] |
| Cost per year, US$ | 26 500 | 32 000 | 63 592 | 196 588 | 78 858 | 51 272 |
| **Sociodemographics** | | | | | | |
| Age, years | 71* | 73* | 49* | 65† | 37* | 51* |
| Sex, female | 52% | 57% | 100% | 39% | 66% | 65% |
| **Decline analysis** | | | | | | |
| Scale | Clinical Dementia Rating Scale-Sum of Boxes | Clinical Dementia Rating Scale-Sum of Boxes | Disease-free survival | Progression-free survival | Multiple Sclerosis Functional Composite | Health Assessment Questionnaire-Disability Index |
| Crude progression rate per year | 0·30 | 0·46 | NA | NA | 0·05 | 0·42 |
| Effect size | 0·19 | 0·26 | NA | NA | 0·20 | 0·25 |
| **Time-to-event analysis** | | | | | | |
| Event | No progression of disability or cognitive impairment | No progression of disability or cognitive impairment | Disease-free survival | Progression-free survival | No progression of disability on Expanded Disability Status Scale | NA |
| Length of follow-up, months | 18 | 18 | 24 | 18 | 24 | 6 |
| Events in treated | 76% | 74% | 86% | 39% | 93% | NA |
| Events in comparator | 68% | 64% | 77% | 7% | 89% | NA |
| Efficacy at time-to-event | 8% | 10% | 9% | 32% | 4% | NA |
| Number needed to treat | 13 | 10 | 11 | 3 | 25 | NA |
| **Safety** | | | | | | |
| Adverse events | Serious ARIA-E | Serious ARIA-E | Severe congestive heart failure | Serious treatment-related adverse events | Any serious adverse event | Serious infections or infestations |
| Rate | 0·3% | 1·5% | 0·5% | 21·4% | 6·9% | 3·0% |

Outcomes and related metrics are disease specific. For details on calculation of the data see the appendix (p 2). NA=not applicable as time-to-disability analyses are not available. ARIA-E=amyloid-related imaging abnormalities with cerebral oedema or sulcal effusion. *Mean. †Median.

*Table 2:* **Efficacy of anti-β amyloid monoclonal antibodies to delay clinically meaningful outcomes and serious adverse events**

| | Alzheimer's disease | Alzheimer's disease | Early stage breast cancer | Lung cancer | Multiple sclerosis | Rheumatoid arthritis |
|---|---|---|---|---|---|---|
| **Drug features** | | | | | | |
| Drug | Lecanemab[17] | Donanemab[18] | Trastuzumab[60] | Pembrolizumab[61] | Ocrelizumab[62] | Tocilizumab[63] |
| Cost per year, US$ | 26 500 | 32 000 | 63 592 | 196 588 | 78 858 | 51 272 |
| **Sociodemographics** | | | | | | |
| Age, years | 71* | 73* | 49* | 65† | 37* | 51* |
| Sex, female | 52% | 57% | 100% | 39% | 66% | 65% |
| **Decline analysis** | | | | | | |
| Scale | Clinical Dementia Rating Scale-Sum of Boxes | Clinical Dementia Rating Scale-Sum of Boxes | Disease-free survival | Progression-free survival | Multiple Sclerosis Functional Composite | Health Assessment Questionnaire-Disability Index |
| Crude progression rate per year | 0·30 | 0·46 | NA | NA | 0·05 | 0·42 |
| Effect size | 0·19 | 0·26 | NA | NA | 0·20 | 0·25 |
| **Time-to-event analysis** | | | | | | |
| Event | No progression of disability or cognitive impairment | No progression of disability or cognitive impairment | Disease-free survival | Progression-free survival | No progression of disability on Expanded Disability Status Scale | NA |
| Length of follow-up, months | 18 | 18 | 24 | 18 | 24 | 6 |
| Events in treated | 76% | 74% | 86% | 39% | 93% | NA |
| Events in comparator | 68% | 64% | 77% | 7% | 89% | NA |
| Efficacy at time-to-event | 8% | 10% | 9% | 32% | 4% | NA |
| Number needed to treat | 13 | 10 | 11 | 3 | 25 | NA |
| **Safety** | | | | | | |
| Adverse events | Serious ARIA-E | Serious ARIA-E | Severe congestive heart failure | Serious treatment-related adverse events | Any serious adverse event | Serious infections or infestations |
| Rate | 0·3% | 1·5% | 0·5% | 21·4% | 6·9% | 3·0% |

Outcomes and related metrics are disease specific. For details on calculation of the data see the appendix (p 2). NA=not applicable as time-to-disability analyses are not available. ARIA-E=amyloid-related imaging abnormalities with cerebral oedema or sulcal effusion. *Mean. †Median.

*Table 2:* **Efficacy of anti-β amyloid monoclonal antibodies to delay clinically meaningful outcomes and serious adverse events**

| | Alzheimer's disease and other dementias | All cancer | Multiple sclerosis | Rheumatoid arthritis |
|---|---|---|---|---|
| **Epidemiology** | | | | |
| Median incident age (5-year groups), years | 75–79 | 65–69 | 30–34 | 50–54 |
| Global prevalence, million cases | 57 (49–65) | 85 (81–89) | 1·9 (1·7–2·1) | 18 (16–20) |
| Global incidence, million cases per year | 9·8 (8·6–11·2) | 24 (22–25) | 0·06 (0·06–0·07) | 1 (0·9–1·1) |
| **Life-years lost** | | | | |
| Per incident case, years | 2·5 | 10·4 | 7·8 | 0·7 |
| Total, million | 25 (6–64) | 244 (229–261) | 0·49 (0·47–0·51) | 0·72 (0·61–0·83) |
| **Years lived with disability** | | | | |
| Per incident case, years | 1·2 | 0·3 | 7·7 | 2·4 |
| Total, million | 12 (8–15) | 8 (6–10) | 0·48 (0·34–0·63) | 2·4 (1·6–3·2) |
| **Disability-adjusted life years** | | | | |
| Per incident case, years | 3·7 | 10·7 | 15·5 | 3·1 |
| Total, million | 36 (17–77) | 252 (236–269) | 1·0 (0·8–1·1) | 3·1 (2·3–4·0) |
| **Cost of disease in Europe, €** | | | | |
| Cost per incident case, millions | 0·21 | 0·07 | 2·05 | 0·37 |
| Annual cost per patient | 35 772 | 13 948 | 51 543 | 18 265 |
| Total cost per year, million | 442 182 | 318 150 | 37 490 | 56 823 |
| **Distribution of costs, €** | | | | |
| Pharmaceuticals | 17 145 (4%) | 51 165 (16%) | Not specified | 4549 (8%)* |
| Direct medical costs | 39 050 (9%) | 112 853 (36%) | 13 636 (36%) | 24 391 (43%) |
| Direct non-medical costs | 149 330 (34%) | Not included | 11 728 (31%) | Not included |
| Productivity loss | Not included | 111 949 (35%) | 12 126 (32%) | 18 979 (33%) |
| Informal care | 236 657 (54%) | 42 183 (13%) | Not included | 8903 (16%) |

Data are estimates (95% CI), unless otherwise specified. Data are from the 2021 Global Burden of Disease study.[98,99] Estimates should be interpreted in light of the diversity of sources across countries and health and social care systems. Not included indicates that a cost component is excluded from the reference. Not specified indicates that the cost component is unavailable at a specified disaggregated level. Index can be found in the appendix (p 4). *Only biological treatment.

*Table 3:* Global burden and cost of disease

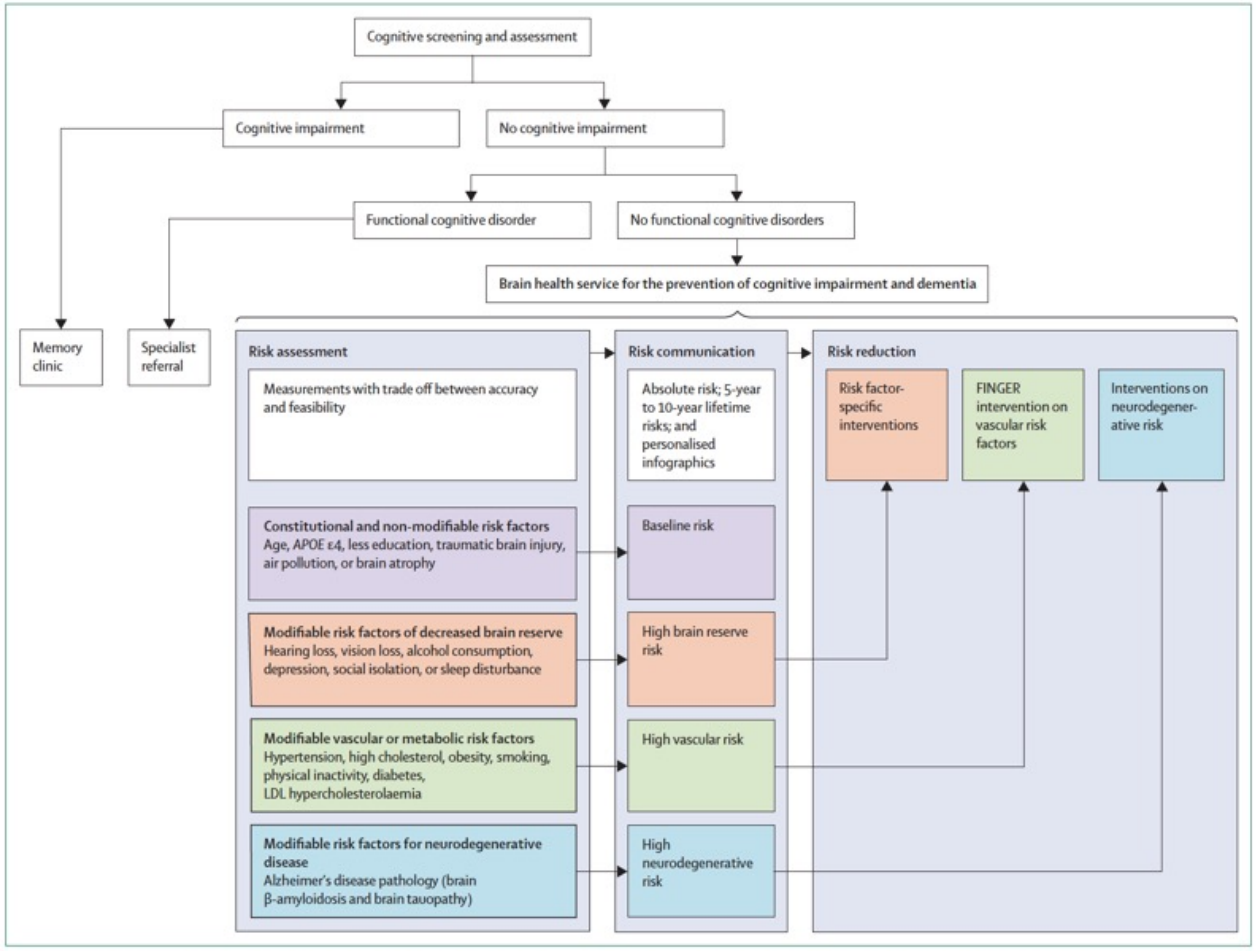



*Figure 2*: **Patient journey for the secondary prevention of cognitive impairment and dementia in individuals without cognitive impairment who are at risk and are under testing in ad-hoc brain health services**

The cognitive impairment branch is addressed in the first and second papers of this Series.[1,2] The functional cognitive disorder branch requires appropriate specialist referral. FINGER=Geriatric Intervention Study to Prevent Cognitive Impairment and Disability.[167]

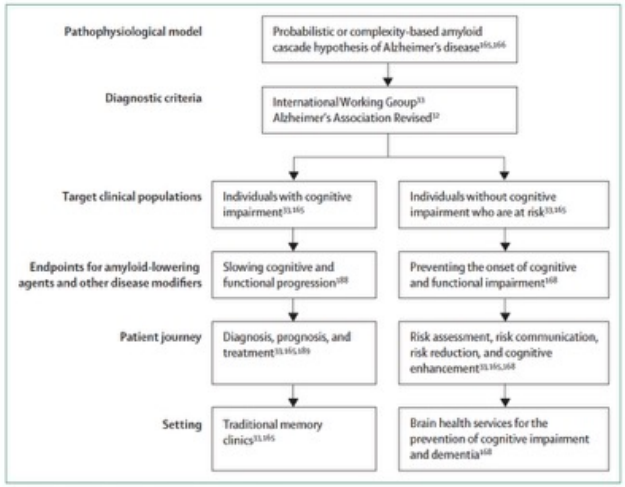



*Figure 3*: **Diagnostic criteria and clinical pathways**

A coherent scientific and clinical narrative is taking shape in Alzheimer's disease research. Modified versions of the amyloid cascade hypothesis leverage notions of probability or complexity and more satisfactorily account for observed clinical and biological variability.[165,166] Although with different emphasis on the constructs of risk condition and disease, the International Working Group 2024 and Alzheimer's Association 2024 diagnostic criteria[33,34] translate these pathophysiological notions into practice. These diagnostic criteria use amyloid cascade biomarkers to diagnose Alzheimer's disease in individuals with cognitive impairment and identify individuals without cognitive impairment who are at risk of cognitive impairment and dementia.[34] Endpoints are different when testing disease modifiers in individuals with and without cognitive impairment. Specific patient journeys for the two clinical groups are available or are being developed for clinical care.[168] These are being, or will be, delivered in ad-hoc settings.[167,168] Reproduced from Frisoni,[190] with permission from BMJ Publishing Group.

## Conclusions

Until recently, the scientific and clinical narratives of Alzheimer's disease were misaligned. Research and drug development were dominated by the amyloid cascade hypothesis, but clinically, diagnostic patient journeys lacked biomarkers related to this pathophysiological framework, and treatments had no effect on amyloid-driven changes. However, this Series shows that, especially in high-income countries, the scientific and clinical narratives around Alzheimer's disease are gradually becoming more coherent—integrating pathophysiology, diagnosis, treatment, and prevention (figure 3).

Many challenges remain. Consensus on what constitutes Alzheimer's disease needs to be reached, similar to efforts with Parkinson's disease and Huntington's disease.[43,191,192] This will impact how Alzheimer's disease is defined in population-based studies and affect incidence and prevalence estimates, identification of risk factor target pathways for innovative drugs, trial design, case selection, and prevention strategies.[193]

This Series paper might not fully explain why Alzheimer's disease treatments are viewed more sceptically than those for other diseases with similar benefits, risks, and costs. Although speculation about historical stigma and the disconnect between public health and basic research is sensible, a substantial body of biological, clinical, public health, and pharmacoeconomics data now allows communities to address the Alzheimer's conundrum[32] as any other treatable and preventable chronic disease. The honest and lively debate among experts will continue. Advances in biomarkers and pharmacological and non-pharmacological prevention methods will support the shared goal of improving cognitive health and quality of life for individuals and communities.

**Camouflage for avoiding detection**
involves strategies to blend with the surroundings, mask one's appearance or movement, or mimic other objects or organisms to avoid being seen by predators or prey.
Common strategies include background matching, where coloration and form resemble the environment; disruptive coloration, which breaks up an animal's outline; disguise, where an organism resembles an inanimate object; and mimicry, where an organism takes on the appearance of another, potentially dangerous, species.

**Aposematism**
is the use of a conspicuous, often bright, warning signal to advertise to potential predators that prey is unpalatable, toxic, or otherwise not worth attacking.
These signals can be visual, such as vibrant colors or patterns (like a monarch butterfly's orange and black), auditory (a rattlesnake's rattle), or even olfactory (a skunk's odor). This strategy benefits both the predator, by avoiding a harmful or unpleasant experience, and the prey, by increasing its chances of survival.

Beute - cryptic

Schutz vor Raubtieren

Beute - warning


# Global selection on insect antipredator coloration

Natural selection has repeatedly led to the evolution of two alternative antipredator color strategies—camouflage to avoid detection and aposematism to advertise unprofitability—but we lack understanding of how ecological context favors one strategy over the other. We conducted a globally replicated predation experiment at 21 sites on six continents to test how predator community, prey community, and visual environment influenced the predation risk of 15,018 artificial paper "moth" prey with cryptic or warning coloration. Results indicated that aposematic strategies fare better in environments with low predation intensity, whereas camouflage strategies are advantaged when other camouflaged prey species are rare and when light levels are low. This study demonstrates how multiple mechanisms shape antipredator strategies, helping to explain the evolution and global distribution of camouflaged and aposematic animals.

Raubtier-Beute Interaktionen

Artificial paper "moth" prey are experimental tools used by scientists to study predator-prey interactions, primarily with birds. These models consist of a paper wing, often a triangle, attached to an edible "body" made of a material like clay, flour, or cake, to record bird attacks. Researchers use these models to investigate the effectiveness of camouflage, warning colors, and disruptive patterns in helping prey avoid predators by observing which designs are attacked more frequently.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We conducted a globally distributed field predation experiment in which we provided wild avian predators in 21 woods and forests across six continents with 15,018 paper “moth” artificial prey targets (~720 per location). These targets were printed with a cryptic bark-like brown color, typical orange-black warning coloration, or similarly conspicuous  but atypical turquoise-black warning coloration. The inclusion of atypical warning-colored prey tested whether orange-black coloration is successful because it is conspicuous or because there is signal generalization of the orange-black colors of Lepidoptera in prey communities. Targets were pinned to trees with a mealworm reward , and we monitored which were consumed. We used palatable meal-worms because attack rates on defended prey are extremely low; this was confirmed with a supporting experiment in which the prey were made unpalatable by injecting meal-worms with quinine. How predators may learn about novel defended (aposematic) prey was inferred from initial predation risk and the rate of change in predation on undefended prey in the context of prior literature.

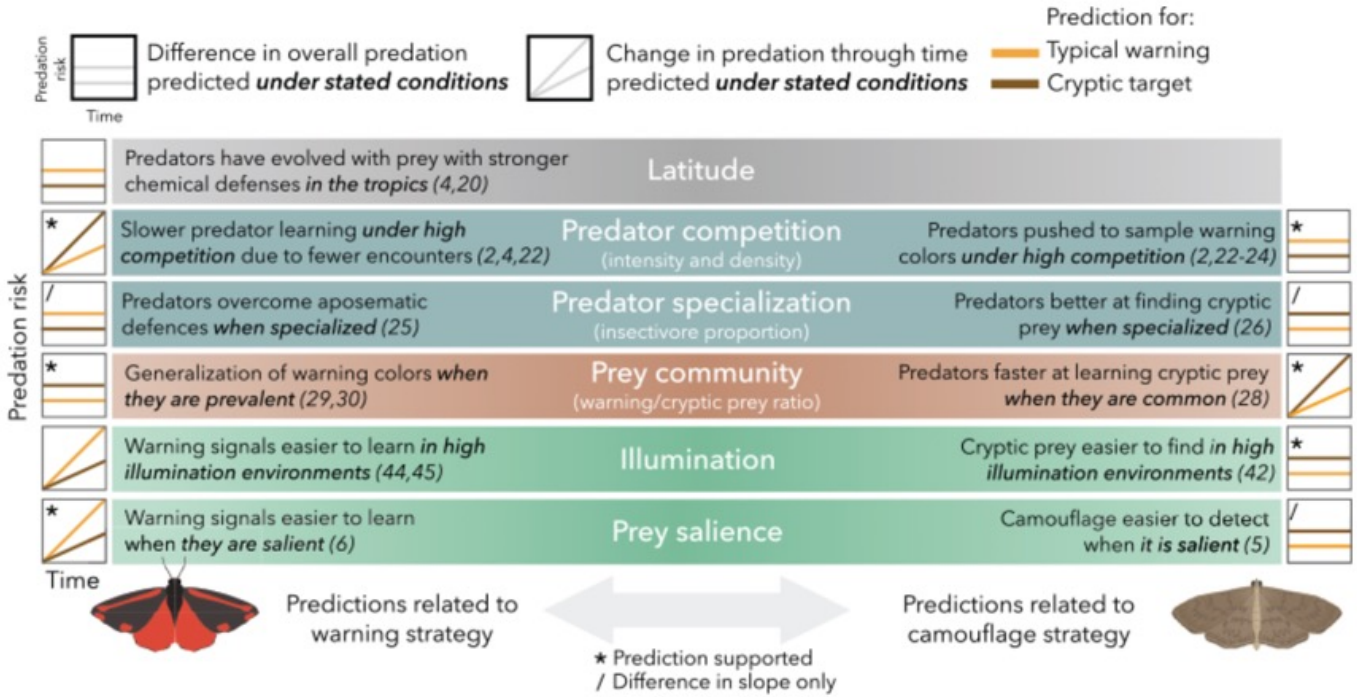


**Fig. 1. Summary of potential ecological variables affecting predation on camouflaged and undefended and defended typical warning-colored (aposematic) prey.** Ecological variables are in white text. Main predictions are summarized in black text, and visualization of predictions is presented in plots, corresponding to changes in either overall predation or learning speed (slope difference). Within plots, brown lines indicate camouflage, and orange lines indicate typical warning color. Predictions supported by this study are indicated with an asterisk. Lepidoptera images: left, *Tyria jacobaeae*; right, *Patania ruralis*. [Credit: iStock.com/jph9362 (left) and iStock.com/ViniSouza128 (right)]

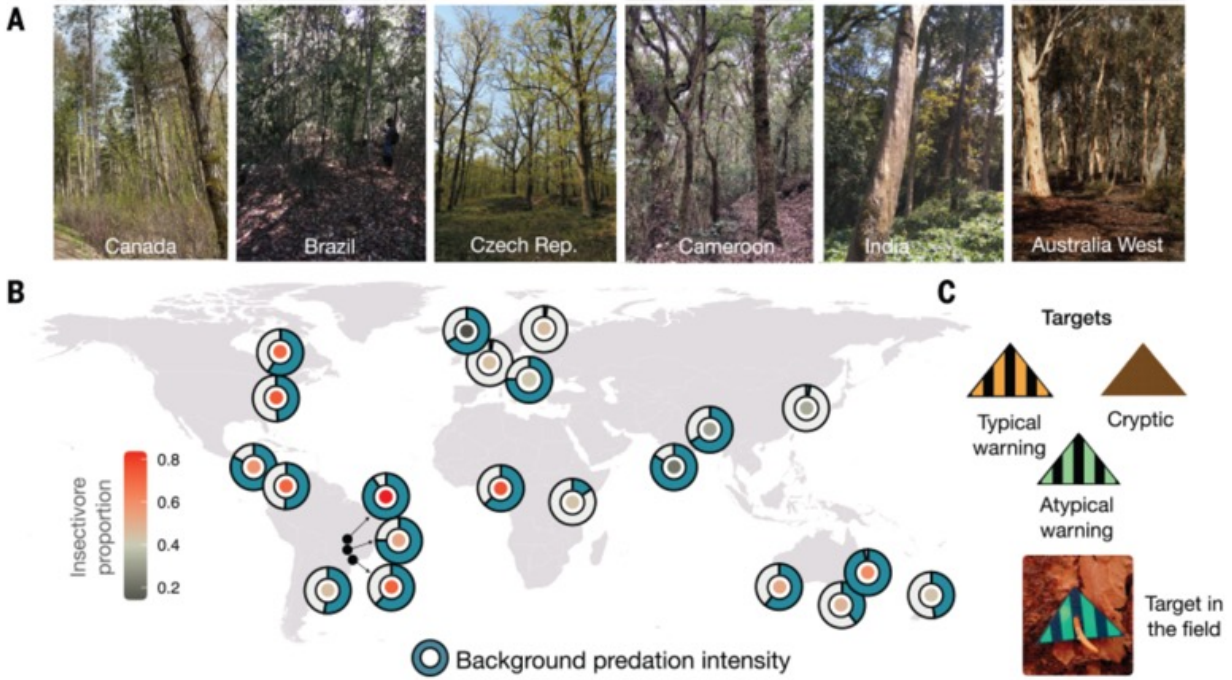


**Fig. 2. Distribution of experiment across the globe and artificial targets used. (A)** Artificial prey were exposed to avian predation in temperate and tropical woods and forests. **(B)** Global distribution of 21 locations. Icons show proportion of insectivorous predators in the inner circle and background predation intensity (percentage consumed in mealworm-only experiment) in the outer circle. **(C)** Three treatments used and an example of the artificial prey used.

**Conclusions**

Our study identified how a complex suite of ecological variables influences the success of crypsis versus warning coloration under natural conditions in terrestrial forest ecosystems across the globe. We found that camouflage effectiveness is highly context dependent. High predator competition initially protects novel cryptic prey but leads to relatively greater predation over time. The success of cryptic strategies also declines when cryptic prey are common, which is consistent with predators learning to search for these prey, and although low illumination improves camouflage initially, this advantage erodes as predator performance improves.

By contrast, warning coloration is generally less sensitive to ecological context but not immune: Predator competition increases initial predation risk and slows learning of the association between warning colors and defense, likely undermining aposematic strategies. Atypical warning colors are also disadvantaged where typical warning-colored prey are common. Although warning-colored prey are more frequent at lower latitudes, this is not a consequence of simple latitudinal shifts in attack rates; instead, it emerges from multiple interacting ecological variables associated with latitude.

Our experiment's ability to compare the importance of multiple ecological variables concludes that predator competition is most critical to the success of camouflage and warning color strategies. One direction for future studies is to investigate this effect through methods to establish the contributions of individual predators to prey survival. Other priorities include testing how ecological predictors influence predator responses to defended prey and assessing variation in predator generalization across communities. Our findings suggest a hypothesis that camouflage, although widespread, may be a less stable defense that is more vulnerable to ecological and anthropogenic change. This predicts that predation outcomes should be more variable for individuals and populations pursuing camouflage strategies compared with warning coloration and that camouflage should be gained and lost more frequently than warning coloration at macroevolutionary scales. Last, our study demonstrates how globally distributed experiments can be key to uncovering complex ecological explanations for the evolution of biological traits.

# I got nose-to-nose with a mountain lion. It was scary — and magical.

PORT ANGELES, Wash. — A mountain lion can sprint up to 50 mph, leap more than 20 feet in the air from a standstill and kill animals 10 times its size. Males can be more than eight feet long from nose to tail and weigh nearly 200 pounds, with paws the size of oven mitts and inches-long teeth and claws.

And right now, according to the animal trackers I am with, there are three of them lurking in the underbrush just steps in front of us.

Suddenly, there is a crash, perhaps 20 yards away. “Did you hear that?” asks Mark Elbroch, who heads up mountain lion research for the conservation group Panthera. “That was probably a cat.”

**Current vs. historical mountain lion range in North America**

Historical range  Current range (2015)